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UTILITY PATENT APPLICATION TRANSMITTAL <small>(Only for new nonprovisional applications under 37 C.F.R. 1.53(b))</small>	Attorney Docket No.	2345.2051-005
	First Named Inventor or Application Identifier	Anna Helgadottir
	Express Mail Label No.	EV 052030802 US

Title of Invention	SUSCEPTIBILITY GENE FOR MYOCARDIAL INFARCTION, STROKE, AND PAOD METHODS OF TREATMENT
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APPLICATION ELEMENTS See MPEP chapter 600 concerning utility patent application contents.	ADDRESS TO: Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
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1. <input type="checkbox"/> Fee Transmittal Form <i>(Submit an original, and a duplicate for fee processing)</i> 2. <input checked="" type="checkbox"/> Specification Total Pages [215] <i>(preferred arrangement set forth below)</i> <ul style="list-style-type: none"> - Descriptive title of the invention - Cross References to Related Applications - Statement Regarding Fed sponsored R & D - Reference to sequence listing, a table, or a computer program listing appendix - Background of the Invention - Brief Summary of the Invention - Brief Description of the Drawings <i>(if filed)</i> - Detailed Description - Claim(s) - Abstract of the Disclosure 3. <input checked="" type="checkbox"/> Drawing(s) (35 U.S.C. 113) Total Sheets [131] <input type="checkbox"/> Fig. of the Drawings for Publication <input type="checkbox"/> <input checked="" type="checkbox"/> No Figure to be Published 4. <input type="checkbox"/> Oath or Declaration Total Pages [] <ul style="list-style-type: none"> a. <input type="checkbox"/> Newly executed (original or copy) b. <input type="checkbox"/> Copy from a prior application (37 C.F.R. 1.63(d)) <i>(for continuation/divisional with Box 17 completed)</i> <ul style="list-style-type: none"> i. <input type="checkbox"/> DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b). 5. <input type="checkbox"/> CD-ROM or CD-R in duplicate, large table or Computer Program <i>(Appendix)</i>	6. <input type="checkbox"/> Nucleotide and/or Amino Acid Sequence Submission <i>(if applicable, all necessary)</i> <ul style="list-style-type: none"> a. <input type="checkbox"/> Computer Readable Form b. <input type="checkbox"/> Paper Copy (identical to computer copy) <div style="text-align: center;">[] Pages</div> c. <input type="checkbox"/> Statements verifying identity of above copies
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17. If a CONTINUING APPLICATION , check appropriate box; supply the requisite information. <div style="display: flex; justify-content: space-between;"> <input type="checkbox"/> Continuation <input type="checkbox"/> Divisional <input checked="" type="checkbox"/> Continuation-in-part (CIP) of prior application No.: 10/769,744 </div> <div style="display: flex; justify-content: space-between;"> Prior application information: Examiner: Group Art Unit: </div> <p style="margin-top: 10px;"> The entire disclosure of the prior application is considered a part of the disclosure of the accompanying application and is hereby incorporated by reference. <i>(Add standard Related Applications section with incorporation by reference to specification or update same)</i> </p>	
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Attorney's Docket No.: 2345.2051-005

SUSCEPTIBILITY GENE FOR MYOCARDIAL INFARCTION, STROKE,
AND PAOD; METHODS OF TREATMENT

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application
10/769,744, filed on January 30, 2004, which is a continuation-in-part of International
5 Application No. PCT/US03/32556, which designated the United States and was filed
on October 16, 2003, published in English, which claims the benefit of U.S.
Provisional Application No. 60/419,433, filed on October 17, 2002 and U.S.
Provisional Application No. 60/449,331, filed on February 21, 2003. The entire
teachings of the above applications are incorporated herein by reference.

10

BACKGROUND OF THE INVENTION

Myocardial infarction (MI) and Acute Coronary Syndrome (ACS), *e.g.*, unstable
angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation
15 myocardial infarction (STEMI), are the leading causes of hospital admissions in
industrialized countries. Cardiovascular disease continues to be the principle cause of
death in the United States, Europe and Japan. The costs of the disease are high both
in terms of morbidity and mortality, as well as in terms of the financial burden on
health care systems.

20 Myocardial infarction generally occurs when there is an abrupt decrease in
coronary blood flow following a thrombotic occlusion of a coronary artery previously
damaged by atherosclerosis. In most cases, infarction occurs when an atherosclerotic
plaque fissures, ruptures or ulcerates and when conditions favor thrombogenesis. In

rare cases, infarction may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic, particularly inflammatory diseases. Medical risk factors for MI include cigarette smoking, diabetes, hypertension and serum total cholesterol levels > 200 mg/dL, elevated serum LDL cholesterol, and low serum HDL cholesterol. Event rates in individuals without a prior history of cardiovascular disease are about 1%. In individuals who have had a first MI or ACS, the risk of a repeat MI within the next year is 10-14%, despite maximal medical management including angioplasty and stent placement.

Atherosclerosis can affect vascular beds in many large and medium arteries. Myocardial infarction and unstable angina (acute coronary syndrome (ACS)) stem from coronary artery atherosclerosis, while ischemic stroke most frequently is a consequence of carotid or cerebral artery atherosclerosis. Limb ischemia caused by peripheral arterial occlusive disease (PAOD) may occur as a consequence of iliac, femoral and popliteal artery atherosclerosis. The atherosclerotic diseases remain common despite the wide-spread use of medications that inhibit thrombosis (aspirin) or treat medical risk factors such as elevated cholesterol levels in blood (statins), diabetes, or hypertension (diuretics and anti-hypertensives).

Atherosclerotic disease is initiated by the accumulation of lipids within the artery wall, and in particular, the accumulation of low-density lipoprotein (LDL) cholesterol. The trapped LDL becomes oxidized and internalized by macrophages. This causes the formation of atherosclerotic lesions containing accumulations of cholesterol-engorged macrophages, referred to as "foam cells". As disease progresses, smooth muscle cells proliferate and grow into the artery wall forming a "fibrous cap" of extracellular matrix enclosing a lipid-rich, necrotic core. Present in the arterial walls of most people throughout their lifetimes, fibrous atherosclerotic plaques are relatively stable. Such fibrous lesions cause extensive remodeling of the arterial wall, outwardly displacing the external, elastic membrane, without reduction in luminal diameter or serious impact on delivery of oxygen to the heart. Accordingly, patients can develop large, fibrous atherosclerotic lesions without luminal narrowing until late in the disease process. However, the coronary arterial

lumen can become gradually narrowed over time and in some cases compromise blood flow to the heart, especially under high demand states such as exercise. This can result in reversible ischemia causing chest pain relieved by rest called stable angina.

5 In contrast to the relative stability of fibrous atherosclerotic lesions, the culprit lesions associated with myocardial infarction and unstable angina (each of which are part of the acute coronary syndrome) are characterized by a thin fibrous cap, a large lipid core, and infiltration of inflammatory cells such as T-lymphocytes and monocyte/macrophages. Non-invasive imaging techniques have shown that most
10 MI's occur at sites with low- or intermediate- grade stenoses, indicating that coronary artery occlusion is due most frequently to rupture of culprit lesions with consequent formation of a thrombus or blood clot and not solely due to luminal narrowing by stenosis. Plaque rupture may be due to erosion or uneven thinning of the fibrous cap, usually at the margins of the lesion where macrophages enter, accumulate, and
15 become activated by a local inflammatory process. Thinning of the fibrous cap may result from degradation of the extracellular matrix by proteases released from activated macrophages. These changes producing plaque instability and risk of MI may be augmented by production of tissue-factor procoagulant and other factors increasing the likelihood of thrombosis.

20 In acute coronary syndrome, the culprit lesion showing rupture or erosion with local thrombosis typically is treated by angioplasty or by balloon dilation and placement of a stent to maintain luminal patency. Patients experiencing ACS are at high risk for a second coronary event due to the multi-vessel nature of coronary artery disease with event rates approaching 10-14% within 12 months after the first incident.

25 The emerging view of MI is as an inflammatory disease of the arterial vessel wall on preexisting chronic atherosclerotic lesions, sometimes triggering rupture of culprit lesions and leading to local thrombosis and subsequent myocardial infarction. The process that triggers and sustains arterial wall inflammation leading to plaque instability is unknown, however, it results in the release into the circulation of tumor
30 necrosis factor alpha and interleukin-6. These and other cytokines or biological mediators released from the damaged vessel wall stimulate an inflammatory response

in the liver causing elevation in several non-specific general inflammatory markers including C-reactive protein. Although not specific to atherosclerosis, elevated C-reactive protein (CRP) and serum amyloid A appear to predict risk for MI, perhaps as surrogates for vessel wall inflammation.

5 Although classical risk factors such as smoking, hyperlipidemia, hypertension, and diabetes are associated with many cases of coronary heart disease (CHD) and MI, many patients do not have involvement of these risk factors. In fact, many patients who exhibit one or more of these risk factors do not develop MI. Family history has long been recognized as one of the major risk factors. Although some of the familial
10 clustering of MI reflects the genetic contribution to the other conventional risk factors, a large number of studies have suggested that there are significant genetic susceptibility factors, beyond those of the known risk factors (Friedlander Y, *et al.*, *Br. Heart J.* 1985; 53:382-7, Shea S. *et al.*, *J. Am. Coll. Cardiol.* 1984; 4:793-801, and Hopkins P.N., *et al.*, *Am. J. Cardiol.* 1988; 62:703-7). Major genetic
15 susceptibility factors have only been identified for the rare Mendelian forms of hyperlipidemia such as a familial hypercholesterolemia.

Genetic risk is conferred by subtle differences in genes among individuals in a population. Genes differ between individuals most frequently due to single nucleotide polymorphisms (SNP), although other variations are also important. SNP
20 are located on average every 1000 base pairs in the human genome. Accordingly, a typical human gene containing 250,000 base pairs may contain 250 different SNP. Only a minor number of SNP are located in exons and alter the amino acid sequence of the protein encoded by the gene. Most SNP have no effect on gene function, while others may alter transcription, splicing, translation, or stability of the mRNA encoded
25 by the gene. Additional genetic polymorphism in the human genome is caused by insertion, deletion, translocation, or inversion of either short or long stretches of DNA. Genetic polymorphisms conferring disease risk may therefore directly alter the amino acid sequence of proteins, may increase the amount of protein produced from the gene, or may decrease the amount of protein produced by the gene.

30 As genetic polymorphisms conferring risk of disease are uncovered, genetic testing for such risk factors is becoming important for clinical medicine. Examples

are apolipoprotein E testing to identify genetic carriers of the apoE4 polymorphism in dementia patients for the differential diagnosis of Alzheimer's disease, and of Factor V Leiden testing for predisposition to deep venous thrombosis. More importantly, in the treatment of cancer, diagnosis of genetic variants in tumor cells is used for the selection of the most appropriate treatment regime for the individual patient. In breast cancer, genetic variation in estrogen receptor expression or heregulin type 2 (Her2) receptor tyrosine kinase expression determine if anti-estrogenic drugs (tamoxifen) or anti-Her2 antibody (Herceptin) will be incorporated into the treatment plan. In chronic myeloid leukemia (CML) diagnosis of the Philadelphia chromosome genetic translocation fusing the genes encoding the Bcr and Abl receptor tyrosine kinases indicates that Gleevec (STI571), a specific inhibitor of the Bcr-Abl kinase should be used for treatment of the cancer. For CML patients with such a genetic alteration, inhibition of the Bcr-Abl kinase leads to rapid elimination of the tumor cells and remission from leukemia.

Many general inflammatory markers predict risk of coronary heart disease, although these markers are not specific to atherosclerosis. For example, Stein (Stein, S., *Am J Cardiol*, 87 (suppl):21A-26A (2001)) discusses the use of any one of the following serum inflammatory markers as surrogates for predicting risk of coronary heart disease including C-reactive protein (CRP), serum amyloid A, fibrinogen, interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9. Elevation in one more of these serum inflammatory markers is not specific to coronary heart disease but also occurs with age or in association with cerebrovascular disease, peripheral vascular disease, non-insulin dependent diabetes, osteoarthritis, bacterial infection, and sepsis.

Serum C-reactive protein (CRP) is viewed as a convenient and sensitive marker of systemic inflammation. Generally CRP is measured in serum samples using commercially available enzyme-linked immunosorbent assays (EIA). Consistent across multiple published studies is the finding of a correlation between increased risk for coronary artery disease with increased serum CRP. For example, in the Women's

Health Study, CRP was measured in 27,939 apparently healthy American women. The cut-off points for quintiles of serum CRP in women were: less than or equal to 0.49, more than 0.49 to 1.08, more than 1.08 to 2.09, more than 2.09 to 4.19, and more than 4.19 mg CRP per liter, see Ridker, P.M. *et al.*, *New England J. Med.*, 347: 1557-1565 (2001). In comparison to the lowest quintile, and even when adjusting for age, every quintile more than 0.49 mg CRP per liter was associated with increased risk for coronary heart disease with the highest relative risk of 4.5 seen for those women in the highest quintile of serum CRP (more than 4.19 mg CRP per liter). A similar correlation between increased serum CRP and increased risk for coronary heart disease in women has been reported (Ridker, P.M *et al.*, *New Engl. J. Med.*, 342:836-843 (2000) and Bermudez, E.A. *et al.*, *Arterioscler. Thromb. Vasc. Biol.*, 22: 1668-1673 (2002)). Men also show a correlation between increased serum inflammatory markers such as CR and increased risk for coronary heart disease has been reported (Doggen, C.J.M. *et al.*, *J. Internal Med.*, 248:406-414 (2000) and Ridker, P.M. *et al.*, *New England J. Med.*, 336: 973-979 (1997)). Quintiles for serum CRP as reported by Doggen *et al.*, were less than 0.65, more than 0.65 to 1.18, more than 1.18 to 2.07, more than 2.07 to 4.23, and more than 4.23 mg CRP per liter. Unlike women, elevated serum CRP correlates with increased relative risk for coronary heart disease only in the 4th and 5th quintiles of CRP (relative risk of 1.7x and 1.9x, respectively).

Serum CRP in women also has been measured in conjunction with lipid markers such as levels of serum low density lipoprotein-cholesterol (LDL-C). In the study by Ridker, P.M. *et al.* (2002), serum CRP and LDL-C are minimally correlated, screening for both serum markers provided better prognostic indication than either alone. Thus, women with serum CRP above median values (more than 1.52 mg CRP per liter) and also serum LDL-C above median values (more than 123.7 mg LDL-C per deciliter) were at highest risk for coronary heart disease.

Elevated CRP or other serum inflammatory markers is also prognostic for increased risk of a second myocardial infarct in patients with a previous myocardial infarct (Retterstol, L. *et al.*, *Atheroscler.*, 160: 433-440 (2002)).

Since CRP is produced in the liver, there is no *a priori* mechanistic explanation for why elevation in CRP and other serum inflammatory markers should be prognostic for coronary artery disease. As discussed by Doggen, C.J.M., *et al.*, one or more of the following factors were speculated to account for the correlation observed:

5 (1) intrinsic inflammation and tissue damage within arterial lesions, (2) prior infection by *Helicobacter pylori* or by *Chlamydia pneumoniae*, (3) release of peptide cytokines including interleukin-6, or (4) activation of the complement system.

The end products of the leukotriene pathway are potent inflammatory lipid mediators derived from arachidonic acid. They can potentially contribute to

10 development of atherosclerosis and destabilization of atherosclerotic plaques through lipid oxidation and/or proinflammatory effects. LTC₄, LTD₄, and LTE₄, are known to induce vasoconstriction. Allen *et al.*, *Circulation*, 97:2406-2413 (1998) described a novel mechanism in which atherosclerosis is associated with the appearance of a leukotriene receptor(s) capable of inducing hyperactivity of human epicardial

15 coronary arteries in response to LTC₄ and LTD₄. LTB₄, on the other hand, is a strong proinflammatory agent. Increased production of these end products, of the leukotriene pathway, could therefore serve as a risk factor for MI and atherosclerosis, whereas both inflammation and vasoconstriction/vasospasm have a well established role in the pathogenesis of MI and atherosclerosis. It has also been shown that a

20 heterozygous deficiency of the 5-LO enzyme in a knockout mouse model decreases atherosclerotic lesion size in LDLR^{-/-} mice by about 95%. (Mehrabian *et al.*, *Circulation Research*. 91:120 (2002)). However, such genetic evidence for leukotriene involvement in MI or atherosclerosis in humans has not been reported. Mehrabian *et al.* did report a very small genetic association study looking for

25 correlation between promoter polymorphisms of 5-LO and carotid intimal thickening in normal individuals. However, their data paradoxically suggest that a lower amount of leukotriene production correlates with carotid atherosclerosis.

SUMMARY OF THE INVENTION

30 As described herein, a gene on chromosome 13q12-13 has been identified as playing a major role in myocardial infarction (MI). This gene, herein after referred to

as the MI gene, comprises nucleic acid that encodes 5-lipoxygenase activating protein (ALOX5AP or FLAP,) herein after referred to as FLAP. The gene has also been shown to play a role in stroke and PAOD.

The invention pertains to methods of treatment (prophylactic and/or therapeutic) for certain diseases and conditions (*e.g.*, MI, ACS, atherosclerosis, stroke, PAOD) associated with FLAP or with other members of the leukotriene pathway (*e.g.*, biosynthetic enzymes or proteins such as FLAP, arachidonate 4-lipoxygenase (5-LO), leukotriene C4 synthase (LTC4S), leukotriene A4 hydrolase (LTA4H), leukotriene B4 12-hydroxydehydrogenase (LTB4DH)); receptors and/or binding agents of the enzymes; and receptors for the leukotrienes LTA4, LTB4, LTC4, LTD4, LTE4, Cys LT1, Cys LT2, including leukotriene B4 receptor 1 (BLT1), leukotriene B4 receptor 2 (BLT2), cysteinyl leukotriene receptor 1 (CysLTR1), cysteinyl leukotriene receptor 2 (CysLTR2). The methods include the following: methods of treatment for myocardial infarction or susceptibility to myocardial infarction; methods of treatment for transient ischemic attack, transient monocular blindness or stroke, or susceptibility to stroke; methods of treatment for claudication, PAOD or susceptibility to PAOD; methods of treatment for acute coronary syndrome (*e.g.*, unstable angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI)); methods for reducing risk of MI, stroke or PAOD in persons with asymptomatic ankle/brachial index less than 0.9; methods for decreasing risk of a second myocardial infarction or stroke; methods of treatment for atherosclerosis, such as for patients requiring treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries (*e.g.*, coronary, carotid, and/or femoral arteries); methods of treatment for asymptomatic ankle/brachial index of less than 0.9; and/or methods for decreasing leukotriene synthesis (*e.g.*, for treatment of myocardial infarction, stroke or PAOD).

In the methods of the invention, a leukotriene synthesis inhibitor is administered to an individual in a therapeutically effective amount. The leukotriene synthesis inhibitor can be an agent that inhibits or antagonizes a member of the leukotriene synthesis pathway (*e.g.*, FLAP, 5-LO, LTC4S, LTA4H, and LTB4DH). For example, the leukotriene synthesis inhibitor can be an agent that inhibits or antagonizes FLAP

polypeptide activity (*e.g.*, a FLAP inhibitor) and/or FLAP nucleic acid expression, as described herein (*e.g.*, a FLAP nucleic acid antagonist). In another embodiment, the leukotriene synthesis inhibitor is an agent that inhibits or antagonizes polypeptide activity and/or nucleic acid expression of another member of the leukotriene biosynthetic pathway (*e.g.*, LTC4S, LTA4H) or that increases breakdown of leukotrienes (*e.g.*, LTB4DH). In preferred embodiments, the agent alters activity and/or nucleic acid expression of FLAP or of 5-LO. Preferred agents include those set forth in the Agent Table herein. In another embodiment, preferred agents can be: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues; or can be zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues. In another embodiment, the agent alters metabolism or activity of a leukotriene (*e.g.*, LTA4, LTB4, LTC4, LTD4, LTE4, Cys LT1, Cys LT2), such as leukotriene antagonists or antibodies to leukotrienes, as well as agents which alter activity of a leukotriene receptor (*e.g.*, BLT1, BLT2, CysLTR1, and CysLTR2).

In certain embodiments of the invention, the individual is an individual who has at least one risk factor, such as an at-risk haplotype for myocardial infarction, stroke or PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; an at-risk polymorphism in the 5-LO gene promoter, diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; a past or current smoker; transient ischemic attack;

transient monocular blindness; carotid endarterectomy; asymptomatic carotid stenosis; claudication; limb ischemia leading to gangrene, ulceration or amputation; a vascular or peripheral artery revascularization graft; an elevated inflammatory marker (*e.g.*, a marker such as C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, 5 a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO), and N-tyrosine); increased LDL cholesterol and/or decreased HDL 10 cholesterol; increased leukotriene synthesis; and/or at least one previous myocardial infarction, ACS, stable angina, previous transient ischemic attack, transient monocular blindness, or stroke, asymptomatic carotid stenosis or carotid endarterectomy, atherosclerosis, requires treatment for restoration of coronary artery blood flow (*e.g.*, angioplasty, stent, revascularization procedure).

15 The invention additionally pertains to methods of assessing an individual for an increased risk of MI, ACS, atherosclerosis, stroke, or PAOD, by assessing a level of a leukotriene metabolite (*e.g.*, LTE₄, LTD₄, LTB₄) in the individual (*e.g.*, in a sample of blood, serum, plasma or urine). An increased level of leukotriene metabolite is indicative of an increased risk. The invention also encompasses methods of assessing 20 an individual for an increased risk of MI, ACS, atherosclerosis, stroke, transient ischemic attack, transient monocular blindness, asymptomatic carotid stenosis, PAOD, claudication, or limb ischemia, by stimulating production of a leukotriene or a leukotriene metabolite in a test sample from the individual (*e.g.*, a sample comprising neutrophils), using a calcium ionophore, and comparing the level of the leukotriene or 25 leukotriene metabolite with a control level. A level of production of the leukotriene or leukotriene metabolite that is significantly greater than the control level, is indicative of increased risk.

 The invention further pertains to methods of assessing response to treatment with a leukotriene synthesis inhibitor, by assessing a level of a leukotriene or 30 leukotriene metabolite in the individual before treatment, and comparing the level to a level of the leukotriene or leukotriene metabolite assessed during or after treatment.

A level that is significantly lower during or after treatment, than before treatment, is indicative of efficacy of the treatment with the leukotriene synthesis inhibitor. The invention additionally pertains to methods of assessing response to treatment with a leukotriene synthesis inhibitor, by stimulating production of a leukotriene or a
5 leukotriene metabolite in a first test sample from the individual (e.g., a sample comprising neutrophils) before treatment, using a calcium ionophore, and comparing the level of the leukotriene or leukotriene metabolite with a level of production of the leukotriene or leukotriene in a second test sample from the individual, during or after treatment. A level of production of the leukotriene or leukotriene metabolite in the
10 second test sample that is significantly lower than the level in the first test sample, is indicative of efficacy of the treatment. Similarly, the invention encompasses methods of assessing response to treatment with a leukotriene synthesis inhibitor, by assessing a level of an inflammatory marker in the individual before treatment, and during or after treatment. A level of the inflammatory marker during or after
15 treatment, that is significantly lower than the level of inflammatory marker before treatment, is indicative of efficacy of the treatment.

The invention also pertains to use of leukotriene synthesis inhibitors for the manufacture of a medicament for the treatment of MI, ACS, stroke, PAOD, and/or atherosclerosis, as described herein, as well as for the manufacture of a medicament
20 for the reduction of leukotriene synthesis.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments
25 of the invention.

FIG. 1 shows the results from a haplotype association case-control analysis of 437 female MI patients versus 721 controls using combinations 4 and 5 microsatellite markers to define the test haplotypes. The *p*-value of the association is plotted on the y-axis and position of markers on the x-axis. Only haplotypes that show association
30 with a *p*-value $< 10^{-5}$ are shown in the figure. The most significant microsatellite marker haplotype association is found using markers DG13S1103, DG13S166,

DG13S1287, DG13S1061 and DG13S301, with alleles 4, 0, 2, 14 and 3, respectively (p -value of 1.02×10^{-7}). Carrier frequency of the haplotype is 7.3% in female MI patients and 0.3% in controls. The segment that is common to all the haplotypes shown in the figure includes only one gene, FLAP.

5 FIG. 2 shows the alleles of the markers defining the most significant microsatellite marker haplotypes. The segment defined with a black square is common to all the of most significantly associated haplotypes. The FLAP nucleic acid is located between makers DG13S166 and D13S1238. Two marker haplotype involving alleles 0 and -2 for markers DG13S166 and D13S1238, respectively, is
10 found in excess in patients. Carrier frequency of this haploype is 27% in patients and 15.4% in controls (p -value 1×10^{-3}). Therefore, association analysis confirms that the most tightly MI-associated gene within the linkage peak is FLAP.

 FIG. 3 shows the relative location of key SNPs and exons of the ALOX5AP/FLAP gene (exons shown in vertical rectangles). Haplotype length varies
15 between 33 to 68 kb.

 FIG. 4 shows the amino acid sequence of FLAP (SEQ ID NO:2) and the mRNA of FLAP (SEQ ID NO: 3).

 FIG. 5 shows a significant positive correlation between serum LTE4 levels and serum CRP levels.

20 FIG. 6.1-6.82 show the genomic sequence of the FLAP gene (SEQ ID NO: 1).

 FIG. 7 depicts LTB4 production of ionomycin stimulated neutrophils from MI patients ($n=41$) and controls ($n=35$). The log-transformed (mean + SD) values measured at 15 and 30 minutes of stimulated cells are shown. (7.1) LTB4 production in MI patients and controls. The difference in the mean values between patients and
25 the controls is tested using a two-sample t-test of the log-transformed values. (7.2) LTB4 production in MI male carriers and non-carriers of haplotype A4. Mean values of controls are included for comparison. Of note, males with the haplotype A4 produce the highest amounts of LTB4 ($p<0.005$ compared to controls). (7.3). Schematic representation of the 5-LO pathway with leukotriene bioactive products.

FIG. 8.1-8.40 show the sequences of the FLAP nucleic acid flanking the SNPs that were identified by sequencing samples from patients (SEQ ID NOs: 506-717).

FIG. 9 shows a schematic view of the chromosome 13 linkage region showing the FLAP gene. (9.1) The linkage scan for female MI patients and the one LOD drop region that includes the FLAP gene; (9.2) Microsatellite association for all MI patients: single marker association and two, three, four and five marker haplotype association. The arrows indicate the location of the most significant haplotype association across the FLAP gene in males and females. (9.3) The FLAP gene structure, with exons shown as cylinders, and the location of all the SNPs typed in the region (vertical lines). The vertical lines indicate the position of the microsatellites (shown in 9.2) and SNPs (shown in 9.3) used in the analysis.

FIG. 10 shows a linkage scan using framework microsatellite markers on chromosome 13 for male patients with ischemic stroke or TIA (n=342 in 164 families at 6 meioses). The LOD score is expressed on the y axis and the distance from the pter in Kosambi cM on the x axis.

FIG. 11 shows a pairwise linkage disequilibrium (LD) between SNPs in a 60 kb region encompassing FLAP. The markers are plotted equidistantly. Two measures of LD are shown: D' in the upper left triangle and P values in the lower right triangle. Shaded lines indicate the positions of the exons of *FLAP* and the stars indicate the location of the markers of the at-risk haplotype A4. Scales for the LD strength are provided for both measures to the right.

DETAILED DESCRIPTION OF THE INVENTION

Extensive genealogical information has been combined with powerful gene sharing methods to map a gene on chromosome 13q12-13 that is associated with myocardial infarction. A genome wide search for susceptibility genes for MI, using a framework map of 1000 microsatellite markers, revealed a locus suggestive of linkage on 13q12-13. Sixty families with 159 female MI patients that clustered within and including 6 meiotic events were used in linkage analysis. At first, only female MI patients were used in the linkage analysis in an effort to enrich for patients with stronger genetic factors

contributing to their risk for MI. The epidemiological study of a population-based sample of Icelandic MI patients had previously suggested that the genetic factors for MI might be stronger for females than males, as the relative risk for siblings of female MI patients was significantly higher than the relative risk for siblings of male probands (1.59 (CI 1.47 - 1.73) vs. 1.35 (CI 1.28 - 1.42)) (unpublished data). The highest LOD score (2.5) was found at marker D13S289. The LOD score results for the families remained the same after adding 14 microsatellite markers to the candidate region. The inclusion of the additional markers increased the information on sharing by descent from 0.7 to 0.8, around the markers that gave the highest LOD scores. This linkage analysis mapped a gene contributing to MI to chromosome 13q12-13.

The candidate MI locus on chromosome 13q12-13 was then finely mapped with microsatellite markers. Patients with myocardial infarction and controls were initially genotyped with microsatellite markers with an average spacing between markers of less than 100 kb over the 12Mb candidate region. Initial haplotype association analysis that included all genotyped microsatellite markers across the MI candidate locus, resulted in several extended haplotypes composed of 4 and 5 microsatellite markers that were significantly associated with female MI (see, *e.g.*, Tables 14 and 15 below). A region common to all these extended haplotypes, is defined by markers DG13S166 and D13S1238. This region includes only one gene, the FLAP nucleic acid sequence. The two marker haplotype involving alleles 0 and -2 for markers DG13S166 and D13S1238, respectively, was found in excess in patients. Specific variants of the gene were then sought that were associated with MI.

In order to screen for SNPs in the FLAP gene, the whole gene was sequenced, both exons and introns. Initially, 9 SNPs identified within the gene were genotyped in patients and controls. Additional microsatellite markers close to or within the FLAP gene were also genotyped in all patients and controls. Five publicly known SNPs that are located within a 200 kb distance 5' to the FLAP gene were also genotyped in patients and controls. Haplotype association analysis in this case-control study including these additional markers showed several different variants of the same haplotype that were all significantly associated with female MI (see, *e.g.*, Table 8). Table 9 shows two haplotypes that are representative of these female MI risk haplotypes which are referred to herein as the female MI "at risk" haplotypes. The relative risk for male MI patients

that had the female MI-“at risk” haplotype was increased (see, *e.g.*, Table 9), indicating that the female MI-“at risk” haplotype also increased the risk of having an MI in males. These results further strengthened the hypothesis that the FLAP gene was an MI susceptibility gene.

5

SNP haplotype association to MI, and subsequently to stroke and PAOD

In an effort to identify haplotypes involving only SNP markers that associate with MI, additional SNPs were identified by sequencing the FLAP gene and the region flanking the gene. Currently, a total of 45 SNPs in 1343 patients and 624 unrelated
10 controls have been genotyped. Two correlated series of SNP haplotypes have been observed in excess in patients, denoted as A and B in Table 7. The length of the haplotypes varies between 33 and 69 kb, and the haplotypes cover one or two blocks of linkage disequilibrium. Both series of haplotypes contain the common allele G of the SNP SG13S25. All haplotypes in the A series contain the SNP SG13S114, while all
15 haplotypes in the B series contain the SNP SG13S106. In the B series, the haplotypes B4, B5, and B6 have a relative risk (RR) greater than 2 and with allelic frequencies above 10%. The haplotypes in the A series have slightly lower RR and lower p-values, but higher frequency (15-16%). The haplotypes in series B and A are strongly correlated, *i.e.*, the haplotypes in B define a subset of the haplotypes in A. Hence,
20 haplotypes in series B are more specific than A. However, haplotypes in series A are more sensitive, *i.e.*, they capture more individuals with the putative mutation, as is observed in the population attributable risk which is less for B than for A. Furthermore, these haplotypes show similar risk ratios and allelic frequencies for early-onset patients (defined as onset of first MI before the age of 55) and for both genders. In addition,
25 analyzing various groups of patients with known risk factors, such as hypertension, high cholesterol, smoking and diabetes, does not reveal any significant correlation with these haplotypes, suggesting that the haplotypes in the FLAP gene represent an independent genetic susceptibility factor for MI.

Because stroke and PAOD are diseases that are closely related to MI (all occur on
30 the basis of atherosclerosis), the SNP haplotype in the FLAP gene that confers risk to MI was assessed to determine whether it also conferred risk of stroke and/or PAOD. Table 20 shows that haplotype A4 increases the risk of having a stroke to a similar extent as it

increases the risk of having an MI. Although not as significantly, haplotype A4 also confers risk of developing PAOD.

The FLAP nucleic acid encodes a 5-lipoxygenase activating protein, which, in combination with 5-lipoxygenase (5-LO), is required for leukotriene synthesis. FLAP
5 acts coordinately with 5-LO to catalyze the first step in the synthesis of leukotrienes from arachidonic acid. It catalyzes the conversion of arachidonic acid to 5(S)-hydroperoxy-6-trans-8,11,14-cis-eicosatetraenoic acid (5-HPETE), and further to the allylic epoxide 5 (S)-trans7,9 trans 11,14-cis-eicosatetraenoic acid (leukotriene A4, LTA4).

The leukotrienes are a family of highly potent biological mediators of
10 inflammatory processes produced primarily by bone marrow derived leukocytes such as monocytes, macrophages, and neutrophils. Both FLAP and 5-LO are detected within atherosclerosis lesions (Proc Natl Acad Sci U S A. 2003 Feb 4;100(3):1238-43.), indicating that the vessel itself can be a source of leukotrienes. It was found at first that the MI-risk FLAP haplotype was associated with higher serum leukotriene levels. Increased
15 production of leukotriene in individuals with pre-existing atherosclerosis lesions may lead to plaque instability or friability of the fibrous cap leading to local thrombotic events. If this occurs in coronary artery arteries it leads to MI or unstable angina. If it occurs in the cerebrovasculature it leads to stroke or transient ischemic attack. If it occurs in large arteries to the limbs, it causes or exacerbates limb ischemia in persons
20 with peripheral arterial occlusive disease (PAOD). Therefore, those with genetically influenced predisposition to produce higher leukotriene levels have higher risk for events due to pre-existing atherosclerosis such as MI.

Inhibitors of FLAP function impede translocation of 5-LO from the cytoplasm to the cell membrane and inhibit activation of 5-LO and thereby decrease leukotriene
25 synthesis.

As a result of these discoveries, methods are now available for the treatment of myocardial infarction (MI) and acute coronary syndrome (ACS), as well as stroke and PAOD, through the use of leukotriene inhibitors, such as agents that inhibit leukotriene biosynthesis or antagonize signaling through leukotriene receptors. The term, "treatment"
30 as used herein, refers not only to ameliorating symptoms associated with the disease or condition, but also preventing or delaying the onset of the disease or condition; preventing or delaying the occurrence of a second episode of the disease or condition;

and/or also lessening the severity or frequency of symptoms of the disease or condition. In the case of atherosclerosis, "treatment" also refers to a minimization or reversal of the development of plaques. Methods are additionally available for assessing an individual's risk for MI, ACS, stroke or PAOD. In a preferred embodiment, the individual to be
5 treated is an individual who is susceptible (at increased risk) for MI, ACS, stroke or PAOD, such as an individual who is in one of the representative target populations described herein.

REPRESENTATIVE TARGET POPULATIONS

10 In one embodiment of the invention, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has an at-risk haplotype in FLAP, as described herein. In one embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S377, SG13S106, SG13S32 and SG13S35 at the 13q12-13 locus. In another embodiment, a
15 haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S106, SG13S30 and SG13S42 at the 13q12 locus. In a third embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S25, SG13S106, SG13S30 and SG13S42 at the 13q12-13 locus. In a fourth embodiment, a haplotype
20 associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S114, SG13S89 and SG13S32 at the 13q12-13 locus. In a fifth embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S25, SG13S114, SG13S89 and SG13S32 at the 13q12-13 locus. Additional haplotypes associated with a
25 susceptibility to myocardial infarction, ACS, stroke or PAOD include the haplotypes shown in Tables 4, 8, 9, 14, 15, 17 and 19, as well as haplotypes comprising markers shown in Table 13.

Increased risk for MI, ACS, stroke or PAOD in individuals with a FLAP at-risk haplotype is logically conferred by increased production of leukotrienes in the arterial
30 vessel wall or in bone-marrow derived inflammatory cells within the blood and/or arterial vessel wall. It is shown herein that FLAP at-risk haplotypes are associated with higher production of LTB4 *ex vivo*. It is further shown herein that serum leukotriene

levels (specifically, leukotriene E4) correlate with serum CRP levels in myocardial infarction patients. FLAP genetic variation may drive high leukotriene levels (within the blood vessel and/or systemically), which in turn may drive higher CRP levels which has been shown as a risk factor for MI. Accordingly, individuals with a FLAP at-risk
5 haplotype are likely to have elevated serum CRP as well as other serum inflammatory markers. The level of serum CRP or other serum inflammatory markers can be used as a surrogate for the level of arterial wall inflammation initiated by lipid deposition and atherogenesis conferred by the presence of the at-risk FLAP haplotype.

In another embodiment of the invention, an individual who is at risk for MI,
10 ACS, stroke or PAOD is an individual who has a polymorphism in a FLAP gene, in which the presence of the polymorphism is indicative of a susceptibility to MI, ACS, stroke or PAOD. The term “gene,” as used herein, refers to not only the sequence of nucleic acids encoding a polypeptide, but also the promoter regions, transcription enhancement elements, splice donor/acceptor sites, and other non-transcribed nucleic
15 acid elements. Representative polymorphisms include those presented in Table 13, below.

In a further embodiment of the invention, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has an at-risk polymorphism in the 5-LO gene in the promoter region, as described herein.

20 In a fourth embodiment, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has an elevated inflammatory marker. An “elevated inflammatory marker,” as used herein, is the presence of an amount of an inflammatory marker that is greater, by an amount that is statistically significant, than the amount that is typically found in control individual(s) or by comparison of disease risk in a
25 population associated with the lowest band of measurement (*e.g.*, below the mean or median, the lowest quartile or the lowest quintile) compared to higher bands of measurement (*e.g.*, above the mean or median, the second, third or fourth quartile; the second, third, fourth or fifth quintile). An “inflammatory marker” refers to a molecule that is indicative of the presence of inflammation in an individual, for example, C-
30 reactive protein (CRP), serum amyloid A, fibrinogen, leukotriene levels (*e.g.*, leukotriene B4, leukotriene C4), leukotriene metabolites (*e.g.*, leukotriene E4), interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble

intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO), N-tyrosine) or other markers (see, *e.g.*, Doggen, C.J.M. *et al.*, *J. Internal Med.*, 248:406-414 (2000); Ridker, P.M. *et al.*, *New Englnd. J. Med.* 1997: 336: 973-979, Rettersol, L. *et al.*, 2002: 160:433-440; Ridker, P.M. *et. al.*, *New England. J. Med.*, 2002: 347: 1557-1565; Bermudez, E.A. *et .al.*, *Arterioscler. Thromb. Vasc. Biol.* , 2002: 22:1668-1673). In certain embodiments, the presence of such inflammatory markers can be measured in serum or urine.

In a fifth embodiment, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has increased LDL cholesterol and/or decreased HDL cholesterol levels. For example, the American Heart Association indicates that an LDL cholesterol level of less than 100 mg/dL is optimal; from 100-129 mg/dL is near/above optimal; from 130-159 mg/dL is borderline high; from 160-189 is high; and from 190 and up is very high. Therefore, an individual who is at risk for MI, ACS, stroke or PAOD because of an increased LDL cholesterol level is, for example, an individual who has more than 100 mg/dL cholesterol, such as an individual who has a near/above optimal level, a borderline high level, a high level or a very high level. Similarly, the American Heart Association indicates that an HDL cholesterol level of less than 40 mg/dL is a major risk factor for heart disease; and an HDL cholesterol level of 60 mg/dL or more is protective against heart disease. Thus, an individual who is at risk for MI, ACS, stroke or PAOD because of a decreased HDL cholesterol level is, for example, an individual who has less than 60 mg/dL HDL cholesterol, such as an individual who has less than 40 mg/dL HDL cholesterol.

In a sixth embodiment, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has increased leukotriene synthesis. "Increased leukotriene synthesis," as used herein, indicates an amount of production of leukotrienes that is greater, by an amount that is statistically significant, than the amount of production of leukotrienes that is typically found in control individual(s) or by comparison of leukotriene production in a population associated with the lowest band of measurement (*e.g.*, below the mean or median, the lowest quartile or the lowest quintile) compared to higher bands of measurement (*e.g.*, above the mean or median, the second, third or fourth quartile; the second, third, fourth or fifth quintile). For example, the FLAP at-risk

haplotypes correlate with increased serum leukotriene synthesis levels, and with increased production of leukotrienes *ex vivo*. An individual can be assessed for the presence of increased leukotriene synthesis by a variety of methods. For example, an individual can be assessed for an increased risk of MI, ACS, stroke, PAOD or
5 atherosclerosis, by assessing the level of a leukotriene metabolite (*e.g.*, LTE4) in a sample (*e.g.*, serum, plasma or urine) from the individual. Samples containing blood, cells, or tissue can also be obtained from an individual and used to assess leukotriene or leukotriene metabolite production *ex vivo* under appropriate assay conditions. An increased level of leukotriene metabolites, and/or an increased level of leukotriene
10 production *ex vivo*, is indicative of increased production of leukotrienes in the individual, and of an increased risk of MI, ACS, stroke, PAOD or atherosclerosis.

In a further embodiment, an individual who is at risk for MI, ACS, or stroke is an individual who has already experienced at least one MI, ACS event or stroke, or who has stable angina, and is therefore at risk for a second MI, ACS event or stroke. In another
15 embodiment, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries.

In further embodiments, an individual who is at risk for MI, stroke or PAOD is an individual having asymptomatic ankle/brachial index of less than 0.9; an individual who
20 is at risk for stroke, is an individual who has had one or more transient ischemic attacks; who has had transient monocular blindness; has had a carotid endarterectomy; or has asymptomatic carotid stenosis; an individual who is at risk for PAOD, is an individual who has (or had) claudication, limb ischemia leading to gangrene, ulceration or amputation, or has had a revascularization procedure.

25 In additional embodiments, an individual who is at risk for MI, ACS, stroke or PAOD is an individual who has diabetes; hypertension; hypercholesterolemia; elevated triglycerides (*e.g.*, > 200 mg/dl); elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and/or is a past or current smoker.

Individuals at risk for MI, ACS, stroke or PAOD may fall into more than one of
30 these representative target populations. For example, an individual may have experienced at least one MI, ACS event, transient ischemic attack, transient monocular blindness, or stroke, and may also have an increased level of an inflammatory marker.

As used therein, the term “individual in a target population” refers to an individual who is at risk for MI, ACS, stroke or PAOD who falls into at least one of the representative target populations described above.

5 ASSESSMENT FOR AT-RISK HAPLOTYPES

A “haplotype,” as described herein, refers to a combination of genetic markers (“alleles”), such as those set forth in Table 13. In a certain embodiment, the haplotype can comprise one or more alleles (e.g., a haplotype containing a single SNP), two or more alleles, three or more alleles, four or more alleles, or five or more alleles. The genetic markers are particular “alleles” at “polymorphic sites” associated with FLAP. A nucleotide position at which more than one sequence is possible in a population (either a natural population or a synthetic population, *e.g.*, a library of synthetic molecules), is referred to herein as a “polymorphic site”. Where a polymorphic site is a single nucleotide in length, the site is referred to as a single nucleotide polymorphism (“SNP”). For example, if at a particular chromosomal location, one member of a population has an adenine and another member of the population has a thymine at the same position, then this position is a polymorphic site, and, more specifically, the polymorphic site is a SNP. Polymorphic sites can allow for differences in sequences based on substitutions, insertions or deletions. Each version of the sequence with respect to the polymorphic site is referred to herein as an “allele” of the polymorphic site. Thus, in the previous example, the SNP allows for both an adenine allele and a thymine allele.

Typically, a reference sequence is referred to for a particular sequence. Alleles that differ from the reference are referred to as “variant” alleles. For example, the reference FLAP sequence is described herein by SEQ ID NO: 1. The term, “variant FLAP”, as used herein, refers to a sequence that differs from SEQ ID NO: 1, but is otherwise substantially similar. The genetic markers that make up the haplotypes described herein are FLAP variants.

Additional variants can include changes that affect a polypeptide, *e.g.*, the FLAP polypeptide. These sequence differences, when compared to a reference nucleotide sequence, can include the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the

generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of a reading frame; duplication of all or a part of a sequence; transposition; or a rearrangement of a nucleotide sequence, as described in detail above. Such sequence changes alter the polypeptide encoded by a FLAP nucleic acid. For example, if the change in the nucleic acid sequence causes a frame shift, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated polypeptide.

Alternatively, a polymorphism associated with a susceptibility to MI, ACS, stroke or PAOD can be a synonymous change in one or more nucleotides (*i.e.*, a change that does not result in a change in the amino acid sequence). Such a polymorphism can, for example, alter splice sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the polypeptide. The polypeptide encoded by the reference nucleotide sequence is the “reference” polypeptide with a particular reference amino acid sequence, and polypeptides encoded by variant alleles are referred to as “variant” polypeptides with variant amino acid sequences.

Haplotypes are a combination of genetic markers, *e.g.*, particular alleles at polymorphic sites. The haplotypes described herein, *e.g.*, having markers such as those shown in Table 13, are found more frequently in individuals with MI, ACS, stroke or PAOD than in individuals without MI, ACS, stroke or PAOD. Therefore, these haplotypes have predictive value for detecting a susceptibility to MI, ACS, stroke or PAOD in an individual. The haplotypes described herein are in some cases a combination of various genetic markers, *e.g.*, SNPs and microsatellites. Therefore, detecting haplotypes can be accomplished by methods known in the art for detecting sequences at polymorphic sites, such as the methods described above.

In certain methods described herein, an individual who is at risk for MI, ACS, stroke or PAOD is an individual in whom an at-risk haplotype is identified. In one embodiment, the at-risk haplotype is one that confers a significant risk of MI, ACS, stroke or PAOD. In one embodiment, significance associated with a haplotype is measured by an odds ratio. In a further embodiment, the significance is measured by a percentage. In one embodiment, a significant risk is measured as an odds ratio of at

least about 1.2, including by not limited to: 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. In a further embodiment, an odds ratio of at least 1.2 is significant. In a further embodiment, an odds ratio of at least about 1.5 is significant. In a further embodiment, a significant increase in risk is at least about 1.7 is significant. In a further
 5 embodiment, a significant increase in risk is at least about 20%, including but not limited to about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 98%. In a further embodiment, a significant increase in risk is at least about 50%. In yet another embodiment, an at-risk haplotype has a p value < 0.05. It is understood however, that identifying whether a risk is medically significant may
 10 also depend on a variety of factors, including the specific disease, the haplotype, and often, environmental factors.

An at-risk haplotype in, or comprising portions of, the FLAP gene, in one where the haplotype is more frequently present in an individual at risk for MI, ACS, stroke or PAOD (affected), compared to the frequency of its presence in a healthy individual
 15 (control), and wherein the presence of the haplotype is indicative of susceptibility to MI, ACS, stroke or PAOD. As an example of a simple test for correlation would be a Fisher-exact test on a two by two table. Given a cohort of chromosomes the two by two table is constructed out of the number of chromosomes that include both of the haplotypes, one of the haplotype but not the other and neither of the haplotypes.

20 In certain embodiments, an at-risk haplotype is an at-risk haplotype within or near FLAP that significantly correlates with a haplotype such as a halotype shown in Table 14; a haplotype shown in Table 15; a haplotype shown in Table 19; haplotype B4; haplotype B5; haplotype B6; haplotype A4; haplotype A5; or haplotype HapB. In other embodiments, an at-risk haplotype comprises an at-risk haplotype within or near
 25 FLAP that significantly correlates with susceptibility to myocardial infarction or stroke. In a particular embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S377, SG13S106, SG13S32 and SG13S35 at the 13q12-13 locus. In another embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or
 30 PAOD comprises markers SG13S99, SG13S25, SG13S106, SG13S30 and SG13S42 at the 13q12-13 locus. In a third embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S25,

SG13S106, SG13S30 and SG13S42 at the 13q12-13 locus. In a fourth embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S114, SG13S89 and SG13S32 at the 13q12-13 locus. In other embodiments, the at-risk haplotype is selected from the

5 group consisting of: haplotype B4, B5, B6, A4 and A5. The at-risk haplotype can also comprise a combination of the markers in the haplotypes B4, B5, B6, A4 and/or A5. In further embodiments, the at-risk haplotype can be haplotype HapB. In other embodiments, the at-risk haplotype comprises a polymorphism shown in Table 13.

Standard techniques for genotyping for the presence of SNPs and/or microsatellite

10 markers can be used, such as fluorescent based techniques (Chen, *et al.*, *Genome Res.* 9, 492 (1999)), PCR, LCR, Nested PCR and other techniques for nucleic acid amplification. In a preferred embodiment, the method comprises assessing in an individual the presence or frequency of SNPs and/or microsatellites in, comprising portions of, the FLAP gene, wherein an excess or higher frequency of the SNPs and/or microsatellites compared to a

15 healthy control individual is indicative that the individual is susceptible to MI, ACS, stroke or PAOD. See, for example, Table 13 (below) for SNPs and markers that can form haplotypes that can be used as screening tools. These markers and SNPs can be identified in at-risk haplotypes. For example, an at-risk haplotype can include microsatellite markers and/or SNPs such as those set forth in Table 13. The presence of

20 the haplotype is indicative of a susceptibility to MI, ACS, stroke or PAOD, and therefore is indicative of an individual who falls within a target population for the treatment methods described herein.

Haplotype analysis involves defining a candidate susceptibility locus using LOD scores. The defined regions are then ultra-fine mapped with microsatellite markers with

25 an average spacing between markers of less than 100 kb. All usable microsatellite markers that are found in public databases and mapped within that region can be used. In addition, microsatellite markers identified within the deCODE genetics sequence assembly of the human genome can be used. The frequencies of haplotypes in the patient and the control groups can be estimated using an expectation-maximization

30 algorithm (Dempster A. *et al.*, 1977. *J. R. Stat. Soc. B*, 39:1-389). An implementation of this algorithm that can handle missing genotypes and uncertainty with the phase can be used. Under the null hypothesis, the patients and the controls are assumed to have

identical frequencies. Using a likelihood approach, an alternative hypothesis is tested, where a candidate at-risk-haplotype, which can include the markers described herein, is allowed to have a higher frequency in patients than controls, while the ratios of the frequencies of other haplotypes are assumed to be the same in both groups. Likelihoods
5 are maximized separately under both hypotheses and a corresponding 1-df likelihood ratio statistic is used to evaluate the statistic significance.

To look for at-risk-haplotypes in the 1-lod drop, for example, association of all possible combinations of genotyped markers is studied, provided those markers span a practical region. The combined patient and control groups can be randomly divided
10 into two sets, equal in size to the original group of patients and controls. The haplotype analysis is then repeated and the most significant p-value registered is determined. This randomization scheme can be repeated, for example, over 100 times to construct an empirical distribution of p-values. In a preferred embodiment, a p-value of <0.05 is indicative of an at-risk haplotype.

15 A detailed discussion of haplotype analysis follows.

Haplotype analysis

Our general approach to haplotype analysis involves using likelihood-based inference applied to NEsted MOdels. The method is implemented in our program
20 NEMO, which allows for many polymorphic markers, SNPs and microsatellites. The method and software are specifically designed for case-control studies where the purpose is to identify haplotype groups that confer different risks. It is also a tool for studying LD structures.

When investigating haplotypes constructed from many markers, apart from
25 looking at each haplotype individually, meaningful summaries often require putting haplotypes into groups. A particular partition of the haplotype space is a model that assumes haplotypes within a group have the same risk, while haplotypes in different groups can have different risks. Two models/partitions are nested when one, the alternative model, is a finer partition compared to the other, the null model, *i.e.*, the
30 alternative model allows some haplotypes assumed to have the same risk in the null model to have different risks. The models are nested in the classical sense that the null model is a special case of the alternative model. Hence traditional generalized

likelihood ratio tests can be used to test the null model against the alternative model. Note that, with a multiplicative model, if haplotypes h_i and h_j are assumed to have the same risk, it corresponds to assuming that $f_i/p_i = f_j/p_j$ where f and p denote haplotype frequencies in the affected population and the control population respectively.

5 One common way to handle uncertainty in phase and missing genotypes is a two-step method of first estimating haplotype counts and then treating the estimated counts as the exact counts, a method that can sometimes be problematic (*e.g.*, see the information measure section below) and may require randomization to properly evaluate statistical significance. In NEMO, maximum likelihood estimates, likelihood
10 ratios and p-values are calculated directly, with the aid of the EM algorithm, for the observed data treating it as a missing-data problem.

NEMO allows complete flexibility for partitions. For example, the first haplotype problem described in the Methods section on Statistical analysis considers testing whether h_1 has the same risk as the other haplotypes h_2, \dots, h_k . Here the
15 alternative grouping is $[h_1], [h_2, \dots, h_k]$ and the null grouping is $[h_1, \dots, h_k]$. The second haplotype problem in the same section involves three haplotypes $h_1 = G0$, $h_2 = GX$ and $h_3 = AX$, and the focus is on comparing h_1 and h_2 . The alternative grouping is $[h_1], [h_2], [h_3]$ and the null grouping is $[h_1, h_2], [h_3]$. If composite alleles exist, one could collapse these alleles into one at the data processing stage, and performed the test as
20 described. This is a perfectly valid approach, and indeed, whether we collapse or not makes no difference if there were no missing information regarding phase. But, with the actual data, if each of the alleles making up a composite correlates differently with the SNP alleles, this will provide some partial information on phase. Collapsing at the data processing stage will unnecessarily increase the amount of missing information. A
25 nested-models/partition framework can be used in this scenario. Let h_2 be split into $h_{2a}, h_{2b}, \dots, h_{2e}$, and h_3 be split into $h_{3a}, h_{3b}, \dots, h_{3e}$. Then the alternative grouping is $[h_1], [h_{2a}, h_{2b}, \dots, h_{2e}], [h_{3a}, h_{3b}, \dots, h_{3e}]$ and the null grouping is $[h_1, h_{2a}, h_{2b}, \dots, h_{2e}], [h_{3a}, h_{3b}, \dots, h_{3e}]$. The same method can be used to handle composite where collapsing at the data processing stage is not even an option since L_C represents multiple haplotypes
30 constructed from multiple SNPs. Alternatively, a 3-way test with the alternative grouping of $[h_1], [h_{2a}, h_{2b}, \dots, h_{2e}], [h_{3a}, h_{3b}, \dots, h_{3e}]$ versus the null grouping of $[h_1,$

$h_{2a}, h_{2b}, \dots, h_{2e}, h_{3a}, h_{3b}, \dots, h_{3e}]$ could also be performed. Note that the generalized likelihood ratio test-statistic would have two degrees of freedom instead of one.

Measuring information

5 Even though likelihood ratio tests based on likelihoods computed directly for the observed data, which have captured the information loss due to uncertainty in phase and missing genotypes, can be relied on to give valid p-values, it would still be of interest to know how much information had been lost due to the information being incomplete. Interestingly, one can measure information loss by considering a two-step
10 procedure to evaluating statistical significance that appears natural but happens to be systematically anti-conservative. Suppose we calculate the maximum likelihood estimates for the population haplotype frequencies calculated under the alternative hypothesis that there are differences between the affected population and control population, and use these frequency estimates as estimates of the observed frequencies
15 of haplotype counts in the affected sample and in the control sample. Suppose we then perform a likelihood ratio test treating these estimated haplotype counts as though they are the actual counts. We could also perform a Fisher's exact test, but we would then need to round off these estimated counts since they are in general non-integers. This test will in general be anti-conservative because treating the estimated counts as if they
20 were exact counts ignores the uncertainty with the counts, overestimates the effective sample size and underestimates the sampling variation. It means that the chi-square likelihood-ratio test statistic calculated this way, denoted by Λ^* , will in general be bigger than Λ , the likelihood-ratio test-statistic calculated directly from the observed data as described in methods. But Λ^* is useful because the ratio Λ/Λ^* happens to be a
25 good measure of information, or $1 - (\Lambda/\Lambda^*)$ is a measure of the fraction of information lost due to missing information. This information measure for haplotype analysis is described in Nicolae and Kong, Technical Report 537, Department of Statistics, University of Statistics, University of Chicago, Revised for *Biometrics* (2003) as a natural extension of information measures defined for linkage analysis, and is
30 implemented in NEMO.

Statistical analysis.

For single marker association to the disease, the Fisher exact test can be used to calculate two-sided p-values for each individual allele. All p-values are presented unadjusted for multiple comparisons unless specifically indicated. The presented frequencies (for microsatellites, SNPs and haplotypes) are allelic frequencies as opposed to carrier frequencies. To minimize any bias due the relatedness of the patients who were recruited as families for the linkage analysis, first and second-degree relatives can be eliminated from the patient list. Furthermore, the test can be repeated for association correcting for any remaining relatedness among the patients, by extending a variance adjustment procedure (*e.g.*, as described in Risch, N. & Teng, J., "The relative power of family-based and case-control designs for linkage disequilibrium studies of complex human diseases I. DNA pooling," *Genome Res.* 8:1278-1288 (1998)) for sibships so that it can be applied to general familial relationships, and present both adjusted and unadjusted p-values for comparison. The differences are in general very small as expected. To assess the significance of single-marker association corrected for multiple testing we carried out a randomisation test using the same genotype data. Cohorts of patients and controls can be randomized and the association analysis redone multiple times (*e.g.*, up to 500,000 times) and the p-value is the fraction of replications that produced a p-value for some marker allele that is lower than or equal to the p-value we observed using the original patient and control cohorts.

For both single-marker and haplotype analyses, relative risk (RR) and the population attributable risk (PAR) can be calculated assuming a multiplicative model (haplotype relative risk model), (Terwilliger, J.D. & Ott, J., *Hum Hered*, 42, 337-46 (1992) and Falk, C.T. & Rubinstein, P, *Ann Hum Genet* 51 (Pt 3), 227-33 (1987)), *i.e.*, that the risks of the two alleles/haplotypes a person carries multiply. For example, if RR is the risk of A relative to a, then the risk of a person homozygote AA will be RR times that of a heterozygote Aa and RR^2 times that of a homozygote aa. The multiplicative model has a nice property that simplifies analysis and computations - haplotypes are independent, *i.e.*, in Hardy-Weinberg equilibrium, within the affected population as well as within the control population. As a consequence, haplotype counts of the affecteds and controls each have multinomial distributions, but with different haplotype frequencies under the alternative hypothesis. Specifically, for two

haplotypes h_i and h_j , $\text{risk}(h_i)/\text{risk}(h_j) = (f_i/p_i)/(f_j/p_j)$, where f and p denote respectively frequencies in the affected population and in the control population. While there is some power loss if the true model is not multiplicative, the loss tends to be mild except for extreme cases. Most importantly, p-values are always valid since they are
 5 computed with respect to null hypothesis.

In general, haplotype frequencies are estimated by maximum likelihood and tests of differences between cases and controls are performed using a generalized likelihood ratio test (Rice, J.A. *Mathematical Statistics and Data Analysis*, 602 (International Thomson Publishing, (1995)). deCODE's haplotype analysis program
 10 called NEMO, which stands for NEsted MOdels, can be used to calculate all the haplotype results. To handle uncertainties with phase and missing genotypes, it is emphasized that we do not use a common two-step approach to association tests, where haplotype counts are first estimated, possibly with the use of the EM algorithm, Dempster, (A.P., Laird, N.M. & Rubin, D.B., *Journal of the Royal Statistical Society B*,
 15 39, 1-38 (1971)) and then tests are performed treating the estimated counts as though they are true counts, a method that can sometimes be problematic and may require randomisation to properly evaluate statistical significance. Instead, with NEMO, maximum likelihood estimates, likelihood ratios and p-values are computed with the aid of the EM-algorithm directly for the observed data, and hence the loss of
 20 information due to uncertainty with phase and missing genotypes is automatically captured by the likelihood ratios. Even so, it is of interest to know how much information is retained, or lost, due to incomplete information. Described herein is such a measure that is natural under the likelihood framework. For a fixed set of markers, the simplest tests performed compare one selected haplotype against all the
 25 others. Call the selected haplotype h_1 and the others h_2, \dots, h_k . Let p_1, \dots, p_k denote the population frequencies of the haplotypes in the controls, and f_1, \dots, f_k denote the population frequencies of the haplotypes in the affecteds. Under the null hypothesis, $f_i = p_i$ for all i . The alternative model we use for the test assumes h_2, \dots, h_k to have the same risk while h_1 is allowed to have a different risk. This implies that while p_1 can be
 30 different from f_1 , $f_i/(f_2 + \dots + f_k) = p_i/(p_2 + \dots + p_k) = \beta_i$ for $i = 2, \dots, k$. Denoting f_1/p_1 by r , and noting that $\beta_2 + \dots + \beta_k = 1$, the test statistic based on generalized likelihood ratios is

$$\Lambda = 2 \left[\ell(\hat{r}, \hat{p}_1, \hat{\beta}_2, \dots, \hat{\beta}_{k-1}) - \ell(1, \tilde{p}_1, \tilde{\beta}_2, \dots, \tilde{\beta}_{k-1}) \right]$$

where ℓ denotes log-likelihood and $\tilde{\cdot}$ and $\hat{\cdot}$ denote maximum likelihood estimates under the null hypothesis and alternative hypothesis respectively. Λ has asymptotically a chi-square distribution with 1-df, under the null hypothesis. Slightly more complicated null and alternative hypotheses can also be used. For example, let h_1 be G0, h_2 be GX and h_3 be AX. When comparing G0 against GX, *i.e.*, this is the test which gives estimated RR of 1.46 and p-value = 0.0002, the null assumes G0 and GX have the same risk but AX is allowed to have a different risk. The alternative hypothesis allows, for example, three haplotype groups to have different risks. This implies that, under the null hypothesis, there is a constraint that $f_1/p_1 = f_2/p_2$, or $w = [f_1/p_1]/[f_2/p_2] = 1$. The test statistic based on generalized likelihood ratios is

$$\Lambda = 2 \left[\ell(\hat{p}_1, \hat{f}_1, \hat{p}_2, \hat{w}) - \ell(\tilde{p}_1, \tilde{f}_1, \tilde{p}_2, 1) \right]$$

that again has asymptotically a chi-square distribution with 1-df under the null hypothesis. If there are composite haplotypes (for example, h_2 and h_3), that is handled in a natural manner under the nested models framework.

LD between pairs of SNPs can be calculated using the standard definition of D' and R^2 (Lewontin, R., *Genetics* 49, 49-67 (1964) and Hill, W.G. & Robertson, A. *Theor. Appl. Genet.* 22, 226-231 (1968)). Using NEMO, frequencies of the two marker allele combinations are estimated by maximum likelihood and deviation from linkage equilibrium is evaluated by a likelihood ratio test. The definitions of D' and R^2 are extended to include microsatellites by averaging over the values for all possible allele combination of the two markers weighted by the marginal allele probabilities. When plotting all marker combination to elucidate the LD structure in a particular region, we plot D' in the upper left corner and the p-value in the lower right corner. In the LD plots the markers can be plotted equidistant rather than according to their physical location, if desired.

Statistical Methods for Linkage Analysis

Multipoint, affected-only allele-sharing methods can be used in the analyses to assess evidence for linkage. Results, both the LOD-score and the non-parametric linkage (NPL) score, can be obtained using the program Allegro (Gudbjartsson *et al.*, *Nat. Genet.* 25:12-3, 2000). Our baseline linkage analysis uses the Spairs scoring function (Whittemore, A.S., Halpern, J. (1994), *Biometrics* 50:118-27; Kruglyak L, *et*

al. (1996), *Am J Hum Genet* 58:1347-63), the exponential allele-sharing model (Kong, A. and Cox, N.J. (1997), *Am J Hum Genet* 61:1179-88) and a family weighting scheme that is halfway, on the log-scale, between weighting each affected pair equally and weighting each family equally. The information measure we use is part of the Allegro program output and the information value equals zero if the marker genotypes are completely uninformative and equals one if the genotypes determine the exact amount of allele sharing by descent among the affected relatives (Gretarsdottir *et al.*, *Am. J. Hom. Genet.* 70:593-603, (2002)). We computed the P-values two different ways and here report the less significant result. The first P-value can be computed on the basis of large sample theory; the distribution of $Z_{lr} = \sqrt{2[\log_e(10)\text{LOD}]}$ approximates a standard normal variable under the null hypothesis of no linkage (Kong, A. and Cox, N.J. (1997), *Am J Hum Genet* 61:1179-88). The second P-value can be calculated by comparing the observed LOD-score with its complete data sampling distribution under the null hypothesis (e.g., Gudbjartsson *et al.*, *Nat. Genet.* 25:12-3, 2000). When the data consist of more than a few families, these two P-values tend to be very similar.

METHODS OF TREATMENT

The present invention encompasses methods of treatment (prophylactic and/or therapeutic, as described above) for MI, ACS, stroke or PAOD in individuals, such as individuals in the target populations described above, as well as for other diseases and conditions associated with FLAP or with other members of the leukotriene pathway (e.g., for atherosclerosis). Members of the "leukotriene pathway," as used herein, include polypeptides (e.g., enzymes, receptors) and other molecules that are associated with production of leukotrienes: for example, proteins or enzymes such as FLAP, 5-LO, other leukotriene biosynthetic enzymes (e.g., leukotriene C4 synthase, leukotriene A4 hydrolase); receptors or binding agents of the enzymes; leukotrienes such as LTA4, LTB4, LTC4, LTD4, LTE4; and receptors of leukotrienes (e.g., leukotriene B4 receptor 1 (BLT1), leukotriene B4 receptor 2 (BLT2), cysteinyl leukotriene receptor 1 (CysLTR1), cysteinyl leukotriene receptor 2 (CysLTR2)).

In particular, the invention relates to methods of treatment for myocardial infarction or susceptibility to myocardial infarction (for example, for individuals in an at-risk population such as those described above); as well as methods of treatment for

acute coronary syndrome (*e.g.*, unstable angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI)); methods for reducing risk of MI, stroke or PAOD in persons with asymptomatic ankle/brachial index less than 0.9; for decreasing risk of a second myocardial infarction; for stroke
5 or susceptibility to stroke; for transient ischemic attack; for transient monocular blindness; for decreasing risk of a second stroke; for PAOD or susceptibility to PAOD; for ABI less than 0.9; for claudication or limb ischemia; for atherosclerosis, such as for patients requiring treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries (*e.g.*, coronary, carotid, and/or femoral
10 arteries); for treatment of asymptomatic ankle/brachial index of less than 0.9; and/or for decreasing leukotriene synthesis (*e.g.*, for treatment of MI, ACS, stroke or PAOD). The invention additionally pertains to use of one or more leukotriene synthesis inhibitors, as described herein, for the manufacture of a medicament for the treatment of MI, ACS, stroke, PAOD and/or atherosclerosis, *e.g.*, using the methods
15 described herein.

In the methods of the invention, a “leukotriene synthesis inhibitor” is used. In one embodiment, a “leukotriene synthesis inhibitor” is an agent that inhibits FLAP polypeptide activity and/or FLAP nucleic acid expression, as described herein (*e.g.*, a nucleic acid antagonist). In another embodiment, a leukotriene synthesis inhibitor is
20 an agent that inhibits polypeptide activity and/or nucleic acid expression of another member of the leukotriene biosynthetic pathway (*e.g.*, 5-LO; LTC4S; LTA4H; LTB4DH). In still another embodiment, a leukotriene synthesis inhibitor is an agent that alters activity or metabolism of a leukotriene (*e.g.*, an antagonist of a leukotriene; an antagonist of a leukotriene receptor). In preferred embodiments, the leukotriene
25 synthesis inhibitor alters activity and/or nucleic acid expression of FLAP or of 5-LO, or alters interaction between FLAP and 5-LO.

Leukotriene synthesis inhibitors can alter polypeptide activity or nucleic acid expression of a member of the leukotriene pathway by a variety of means, such as, for example, by catalytically degrading, downregulating or interfering with the
30 expression, transcription or translation of a nucleic acid encoding the member of the leukotriene pathway; by altering posttranslational processing of the polypeptide; by altering transcription of splicing variants; or by interfering with polypeptide activity

(e.g., by binding to the polypeptide, or by binding to another polypeptide that interacts with that member of the leukotriene pathway, such as a FLAP binding agent as described herein or some other binding agent of a member of the leukotriene pathway; by altering interaction among two or more members of the leukotriene pathway (e.g., interaction between FLAP and 5-LO); or by antagonizing activity of a member of the leukotriene pathway.

Representative leukotriene synthesis inhibitors include the following:

agents that inhibit activity of a member of the leukotriene biosynthetic pathway (e.g., FLAP, 5-LO), LTC4S, LTA4H, such as the agents presented in the Agent Table below; agents that inhibit activity of receptors of members of the leukotriene pathway, such as FLAP receptors, LTA4 receptors, LTB4 receptors, LTC4 receptors, LTD4 receptors, LTE4 receptors, Cys LT1 receptors, Cys LT2 receptors, 5-LO receptors; BLT1; BLT2; CysLTR1; CysLTR2; agents that bind to the members of the leukotriene pathway, such as FLAP binding agents (e.g., 5-LO) or agents that bind to receptors of members of the leukotriene pathway (e.g., leukotriene receptor antagonists); agents that bind to a leukotriene (e.g., to LTA4, LTB4, LTC4, LTD4, LTE4, Cys LT1, Cys LT2); agents that increase breakdown of leukotrienes (e.g., LTB4DH); or other agents that otherwise affect (e.g., increase or decrease) activity of the leukotriene;

antibodies to leukotrienes;

antisense nucleic acids or small double-stranded interfering RNA, to nucleic acids encoding FLAP, 5-LO, or a leukotriene synthetase or other member of the leukotriene pathway, or fragments or derivatives thereof, including antisense nucleic acids to nucleic acids encoding the FLAP, 5-LO or leukotriene synthetase polypeptides, and vectors comprising such antisense nucleic acids (e.g., nucleic acid, cDNA, and/or mRNA, double-stranded interfering RNA, or a nucleic acid encoding an active fragment or derivative thereof, or an oligonucleotide; for example, the complement of one of SEQ ID Nos. 1 or 3, or a nucleic acid complementary to the nucleic acid encoding SEQ ID NO: 2, or fragments or derivatives thereof);

peptidomimetics; fusion proteins or prodrugs thereof; ribozymes; other small molecules; and

5 other agents that alter (*e.g.*, inhibit or antagonize) expression of a member of the leukotriene pathway, such as FLAP or 5-LO nucleic acid expression or polypeptide activity, or that regulate transcription of FLAP splicing variants or 5-LO splicing variants (*e.g.*, agents that affect which splicing variants are expressed, or that affect the amount of each splicing variant that is expressed).

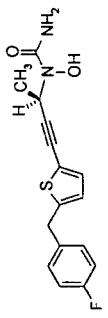
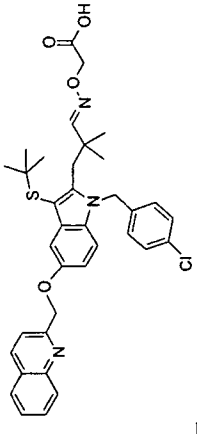
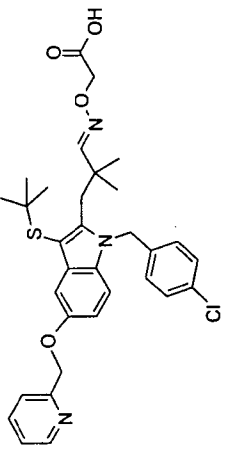
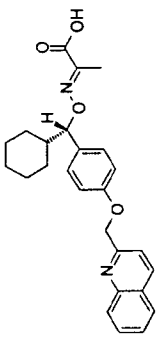
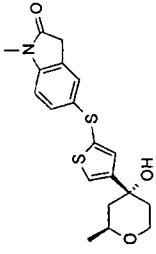
10 More than one leukotriene synthesis inhibitor can be used concurrently, if desired.

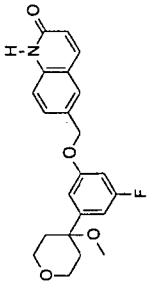
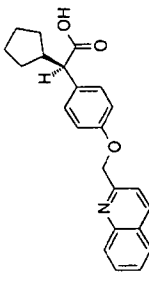
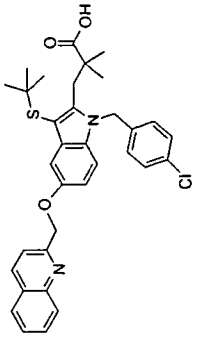
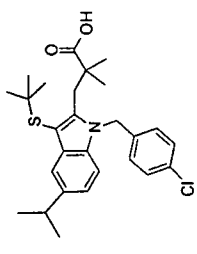
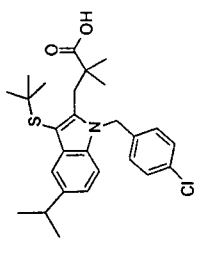

The therapy is designed to alter activity of a FLAP polypeptide, a 5-LO polypeptide, or another member of the leukotriene pathway in an individual, such as by inhibiting or antagonizing activity. For example, a leukotriene synthesis inhibitor
15 can be administered in order to decrease synthesis of leukotrienes within the individual, or to downregulate or decrease the expression or availability of the FLAP nucleic acid or specific splicing variants of the FLAP nucleic acid. Downregulation or decreasing expression or availability of a native FLAP nucleic acid or of a particular splicing variant could minimize the expression or activity of a defective
20 nucleic acid or the particular splicing variant and thereby minimize the impact of the defective nucleic acid or the particular splicing variant. Similarly, for example, a leukotriene synthesis inhibitor can be administered in order to downregulate or decrease the expression or availability of the nucleic acid encoding 5-LO or specific splicing variants of the nucleic acid encoding 5-LO.

25 The leukotriene synthesis inhibitor(s) are administered in a therapeutically effective amount (*i.e.*, an amount that is sufficient to treat the disease or condition, such as by ameliorating symptoms associated with the disease or condition, preventing or delaying the onset of the disease or condition, and/or also lessening the severity or frequency of symptoms of the disease or condition). The amount which
30 will be therapeutically effective in the treatment of a particular individual's disease or condition will depend on the symptoms and severity of the disease, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to

be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test
5 systems.

In preferred embodiments of the invention, the leukotriene synthesis inhibitor agent is an agent that inhibits activity of FLAP and/or of 5-LO. Preferred agents include the following, as set forth in the Agent Table:

Company	Product Name (Code)	Structure	Chemical Name	Patent Ref	Date Patent Issued/ Application Published	MOA
Abbott	aireleuton (ABT-761)		(R)-(+)-N-[3-[5-[(4-fluorophenyl)methyl]-2thienyl]-1methyl-2-propynyl]-N-hydroxurea	US 5288751, US 5288743, US 5616596	2/22/94 04/01/97	5-LPO inhibitor
Abbott	A-81834		3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid	WO9203132, US 5459150	3/5/1992, 10/17/95	FLAP inhibitor
Abbott	A-86886		3-(3-(1,1-dimethylethylthio-5-(pyridin-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid	WO9203132, US 5459150	3/5/1992, 10/17/95	5-LPO inhibitor
Abbott	A-93178					FLAP inhibitor
AstraZeneca	AZD-4407			EP 623614	09/11/94	5-LPO inhibitor

AstraZeneca	ZD-2138		6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4-yl)phenoxy)methyl)-1-methyl-2-(1H)-quinolinone (alternatively NH can be N-methyl)	EP 466452		5-LPO inhibitor
Bayer	BAY-X-1005		(R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-benzeneacetic acid	US 4970215 EP 344519, DE 19880531		FLAP inhibitor
Merck	MK-0591		1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-5-(alpha, alpha-dimethyl-2-quinolinylmethoxy)-1H-indole-2-propanoic acid	EP 419049, US 19890822		FLAP inhibitor
Merck	MK-866		(3-(3-(4-chlorobenzyl)-3-butylthio-5-isopropylindol-2-yl)-2-dimethyl-propanoic acid			5-LPO inhibitor
Merck	MK-886		1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-5-(alpha, alpha-dimethyl-2-quinolinylmethoxy)-1H-indole-2-propanoic acid	EP 419049, US 19890822		5-LPO inhibitor
Pfizer	CJ-13610		4-(3-(4-(2-Methylimidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide			5-LPO inhibitor

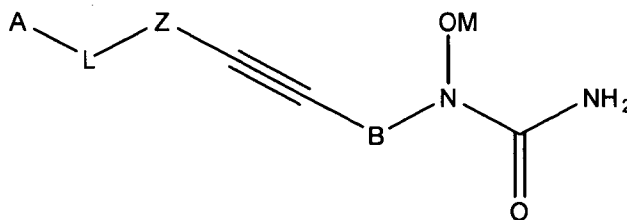
In preferred methods of the invention, the agents set forth in the Agent Table can be used for prophylactic and/or therapeutic treatment for diseases and conditions associated with FLAP or with other members of the leukotriene pathway, or with increased leukotriene synthesis. In particular, they can be used for treatment for myocardial infarction or susceptibility to myocardial infarction, such as for individuals in an at-risk population as described above, (*e.g.*, based on identified risk factors such as elevated cholesterol, elevated C-reactive protein, and/or genotype); for individuals suffering from acute coronary syndrome, such as unstable angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI); methods for reducing risk of MI, stroke or PAOD in persons with asymptomatic ankle/brachial index less than 0.9; for decreasing risk of a subsequent myocardial infarction, such as in individuals who have already had one or more myocardial infarctions; for stroke or susceptibility to stroke; for decreasing risk of a second stroke; for PAOD or susceptibility to PAOD; for treatment of atherosclerosis, such as in patients requiring treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries (*e.g.*, coronary, carotid, and/or femoral arteries); for treatment of asymptomatic ankle/brachial index of less than 0.9; and/or for decreasing leukotriene synthesis (*e.g.*, for treatment of myocardial infarction, ACS, stroke or PAOD

In one preferred embodiment of the invention, the leukotriene synthesis inhibitor is an inhibitor of FLAP such as 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)- α,α -dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)- α -cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, their optically pure enantiomers, salts, chemical derivatives, analogues, or other compounds inhibiting FLAP that effectively decrease leukotriene biosynthesis when administered to humans.

In another preferred embodiment of the invention, the leukotriene synthesis inhibitor is an inhibitor of 5LO such as zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone

otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-
 ((1,1dimethylethylthio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-
 2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-
 phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known
 5 as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, analogues
 or other compounds inhibiting 5-LO that effectively decrease leukotriene biosynthesis
 when administered to humans.

The compound can be represented by the following formula:



10

or a pharmaceutically acceptable salt thereof, wherein M is selected from the group
 consisting of hydrogen, a pharmaceutically acceptable cation, and a
 15 pharmaceutically acceptable metabolically cleavable group; B is a straight or
 branched divalent alkylene group of from one to twelve carbon atoms; Z is
 thiazolyl, optionally substituted with alkyl of from one to six carbon atoms or
 haloalkyl of from one to six carbon atoms; L is selected from the group consisting
 of (a) alkylene of from 1-6 carbon atoms, (b) alkenylene of from 2-6 carbon atoms,
 20 (c) alkynylene of from 2-6 carbon atoms, (d) hydroxyalkyl of 1-6 carbon atoms, (e)
 $>C=O$, (f) $>C=N-OR_1$, where R_1 is hydrogen or C_1 - C_6 alkyl, (g) $-(CHR_1)_n$
 $(CO)(CHR_2)_m$, where n and m are independently selected from an integer from one
 to six and R_1 and R_2 are independently selected from hydrogen and C_1 - C_6 -alkyl,
 (h) $-(CHR_1)_n C=NOR_2$, where R_1 , R_2 and n are as defined above; (i) $-(CHR_1)_n$
 25 $ON=CR_2$, where R_1 , R_2 and n are as: defined above; (j) $-(CHR_1)_n -O-(CHR_2)_m$ -,
 where R_1 , R_2 , n and m are as defined above, (k) $-(CHR_1)_n -NR_2 (CHR_3)_m$ -, where
 R_1 , R_2 , n and m are as defined above and R_3 is selected from hydrogen and C_1 - C_6 -
 alkyl; (l) $-(CHR_1)_n -S- CHR_2)_m$ -, where R_1 , R_2 , n and m are as defined above; and

(m) $-(\text{CHR}_1)_n-(\text{SO}_2)-(\text{CHR}_2)_m-$, where R_1 , R_2 , n and m are as defined above; A is carbocyclic aryl optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, hydroxyalkyl of from one to six carbon atoms, alkoxy of from one to twelve carbon atoms, alkoxyalkoxyl in which the two

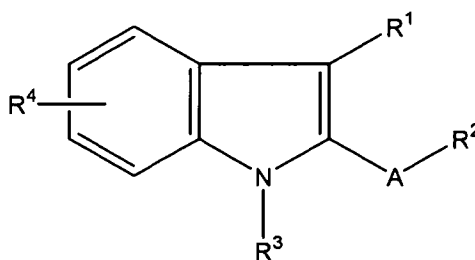
5 alkoxy portions may each independently contain from one to six carbon atoms, alkylthio of from one to six carbon atoms, hydroxy, halogen, cyano, amino, alkylamino of from one to six carbon atoms, dialkylamino in which the two alkyl groups may independently contain from one to six carbon atoms, alkanoylamino of from two to eight carbon atoms, N-alkanoyl-N-alkylamino in which the alkanoyl is

10 of from two to eight carbon atoms and the alkyl group is of from one to six carbon atoms, alkylaminocarbonyl of from two to eight carbon atoms, dialkylaminocarbonyl in which the two alkyl groups are independently of from one to six carbon atoms, carboxyl, alkoxy carbonyl or from two to eight carbon atoms, phenyl, optionally substituted with alkyl of from one to six carbon atoms, haloalkyl

15 of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy or halogen, phenoxy, optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy or halogen, and phenylthio, optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, alkoxy of

20 from one to six carbon atoms, hydroxy or halogen. Preferably, the compound is a compound or pharmaceutically acceptable salt thereof having the name (R)-N-{3-[-5-(4-fluorophenylmethyl)thiazo-2-yl]-1methyl-2-propynyl}-N-hydroxyurea. See U.S. Patent No. 4,615,596, incorporated herein by reference.

25 The compound is represented by the following formula:

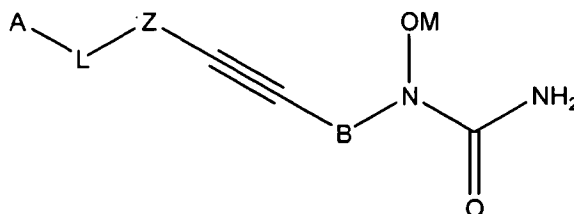


or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of straight or branched divalent alkylene of from one to twelve carbon

atoms and divalent cycloalkylene of from three to eight carbon atoms; R_1 is selected from the group consisting of hydrogen, alkylthio of from one to six carbon atoms, phenylthio, optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen, phenylalkylthio in which the alkyl portion contains from one to six carbon atoms, and the phenyl group is optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen, R_2 is selected from the group consisting of -COOB wherein B is selected from hydrogen, a pharmaceutically acceptable cation, or a metabolically cleavable group, -COOalkyl where the alkyl portion contains from one to six carbon atoms, -COOalkylcarbocyclicaryl where the alkyl portion contains from one to six carbon atoms and the aryl portion is optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen, -CONR₅R₆ wherein R_5 is selected from the group consisting of hydrogen, hydroxyl, alkyl of from one to six carbon atoms, and alkoxy of from one to six carbon atoms, and R_6 is selected from the group consisting of hydrogen and alkyl of from one to six carbon atoms, -COR₆, and -OH; R_3 is selected from the group consisting of phenylalkyl in which the alkyl portion contains from one to six carbon atoms, and the phenyl group is optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen, R_4 is selected from the group consisting of thiazolylalkyloxy in which the alkyl portion contains from one to six carbon atoms, and the heteroaryl portion is optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen, and thiazolyloxy optionally substituted with alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, or halogen.

See U.S. Patent No. 5,288,743, incorporated herein by reference.

The compound can be represented by the formula:

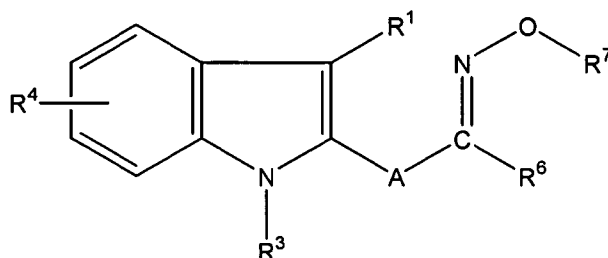


or a pharmaceutically acceptable salt thereof, wherein M is selected from the group consisting of hydrogen, and a pharmaceutically acceptable cation;

- 5 B is a straight or branched divalent alkylene group of from one to twelve carbon atoms; Z is selected from the group consisting of: (a) furyl, optionally substituted with alkyl of from one to six carbon atoms, or haloalkyl of from one to six carbon atoms, and (b) thienyl, optionally substituted with alkyl of from one to six carbon atoms, or haloalkyl of from one to six carbon atoms; and L is alkylene of from 1-6
- 10 carbon atoms; A is phenyl optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, hydroxyalkyl of from one to six carbon atoms, alkoxy of from one to twelve carbon atoms, alkoxyalkoxyl in which the two alkoxy portions may each independently contain from one to six carbon atoms, alkylthio of from one to six carbon atoms, hydroxy, halogen, cyano,
- 15 amino, alkylamino of from one to six carbon atoms, dialkylamino in which the two alkyl groups may independently contain from one to six carbon atoms, alkanoylamino of from two to eight carbon atoms, N-alkanoyl-N-alkylamino in which the alkanoyl is of from two to eight carbon atoms and the alkyl group is of from one to six carbon atoms, alkylaminocarbonyl of from two to eight carbon
- 20 atoms, dialkylaminocarbonyl in which the two alkyl groups are independently of from one to six carbon atoms, carboxyl, alkoxycarbonyl of from two to eight carbon atoms, phenyl, optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy or halogen, phenoxy, optionally substituted with alkyl of from one to six
- 25 carbon atoms, haloalkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy or halogen, or phenylthio, optionally substituted with alkyl of from one to six carbon atoms, haloalkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, hydroxy or halogen. Preferably, the compound is a compound or a pharmaceutically acceptable salt thereof selected from the group
- 30 consisting of: N-{3-(5-(4-fluorophenylmethyl)furyl)-3-butyn-2-yl}-N-hydroxyurea; N-{3-(5-(4-fluorophenylmethyl)-2-thienyl)-1-methyl-2-propynyl}-N-hydroxyurea; (R)-N-{3-(5-(4-fluorophenylmethyl)-2-thienyl)-1-methyl-2-

propynyl}-N-hydroxyurea; and (R)-N-{3-(5-(4-chlorophenylmethyl)-2-thienyl)-1-methyl-2-propynyl}-N-hydroxyurea; (S)-N-{3-[5-(4-fluorophenylmethyl)-2-thienyl]-1-methyl-2-propynyl}-N-hydroxyurea. See U.S. Patent No. 5,288,751, incorporated by reference herein.

5 The compound can be represented by the formula:



10 or a pharmaceutically acceptable salt thereof, wherein A is selected from the group consisting of straight or branched divalent alkylene of one to twelve carbon atoms, straight or branched divalent alkenylene of two to twelve carbon atoms, and divalent cycloalkylene of three to eight carbon atoms; R^1 is alkylthio of one to six carbon atoms; R^6 is selected from the group consisting of hydrogen and alkyl of one to six carbon atoms; R^7 is selected from the group consisting of (carboxyl)alkyl in which the alkyl portion is of one to six carbon atoms, (alkoxycarbonyl)alkyl in which the alkoxycarbonyl portion is of two to six carbon atoms and the alkyl portion is of one to six carbon atoms, (aminocarbonyl)alkyl in which the alkyl portion is of one to six carbon atoms, ((alkylamino)carbonyl)alkyl in which each alkyl portion independently is of one to six carbon atoms, and ((dialkylamino)carbonyl)alkyl in which each alkyl portion independently is of one to six carbon atoms; R^3 is phenylalkyl in which the alkyl portion is of one to six carbon atoms; R^4 is 2-, 3- or 6-quinolylmethoxy, optionally substituted with alkyl of one to six carbon atoms, haloalkyl of one to six carbon atoms, alkoxy of one to twelve carbon atoms, halogen, or hydroxy. Preferably, the compound is selected from the group consisting of: 3-(3-(1,1-dimethylethylthio)-5-(quinolin-2-ylmethoxy)-1-(4-chlorophenylmethyl)-indol-2-yl)-2,2-dimethylpropionaldehyde oxime-O-2

acetic acid; 3-(3-(1,1-dimethylethylthio)-5-(quinolin-2-ylmethoxy)-1-(4-chloro-phenylmethyl) indol-2-yl)-2,2-dimethylpropionaldehyde oxime-O-2-(3-methyl)butyric acid; 3-(3-(1,1-dimethylethylthio)-5-(6,7-dichloroquinolin-2-ylmethoxy)-1-(4-chlorophenylmethyl) indol-2-yl)-2,2-dimethylpropionaldehyde
 5 oxime-O-2-acetic acid; and 3-(3-(1,1-dimethylethylthio)-5-(6-fluoroquinolin-2-ylmethoxy)-1-(4chlorophenylmethyl) indol-2-yl)-2,2-dimethylpropionaldehyde oxime-O-2-propionic acid; or a pharmaceutically acceptable salt or ester thereof. See U.S. Patent No. 5,459,150, incorporated by reference herein.

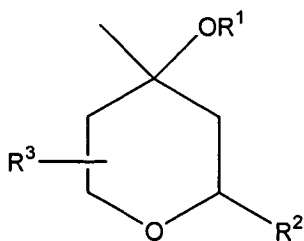
The compound can be represented by the formula:

10

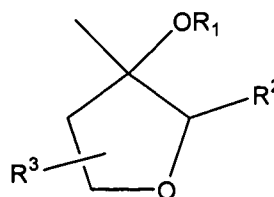


or pharmaceutically acceptable salts thereof, wherein Q is a 9-, 10- or 11-membered bicyclic heterocyclic moiety containing one or two nitrogen heteroatoms
 15 and optionally containing a further heteroatom selected from nitrogen, oxygen and sulphur, and Q may optionally bear up to four substituents selected from halogeno, hydroxy, cyano, formyl, oxo, thioxo, (1-4C)alkyl, (3-4C)alkenyl, (3-4C)alkynyl, (1-4C)alkoxy, fluoro-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (2-5C)alkanoyl, phenyl, benzoyl and benzyl, and wherein said phenyl, benzoyl and benzyl substituents may
 20 optionally bear one or two substituents selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;

X is oxy, thio, sulphinyl or sulphonyl; Ar is phenylene, pyridinediyl, pyrimidinediyl, thiophenediyl, furandiyl, thiazolediyl, oxazolediyl, thiadiazolediyl or oxadiazolediyl which may optionally bear one or two substituents selected from
 25 halogeno, cyano, trifluoromethyl, hydroxy, amino, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino and di-(1-4C)alkylamino; and Q is selected from the groups of the formulae II and III:



II

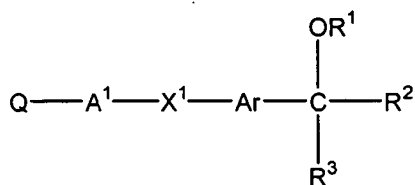


III

wherein R is hydrogen, (2-5C)alkanoyl or benzoyl, and wherein said benzoyl group may optionally bear one or two substituents selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; R is (1-4C)alkyl; and R is hydrogen or (1-4C)alkyl; or R and R are linked to form a methylene, vinylene, ethylene or trimethylene group. Preferably, the compound is selected from the group consisting of: (2S,4R)-4-[5-fluoro-3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]-4-hydroxy-2-ethyltetrahydropyran, (2S,4R)-4-[5-fluoro-3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylsulphonyl)phenyl]-4-hydroxy-2-methyltetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thiazol-5-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylsulphonyl)thiazol-5-yl]tetrahydropyran, (2S,4R)-4-[2-(7-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thiazol-5-yl]-4-hydroxy-2-methyltetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxoindolin-5-ylthio)thiazol-5-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thien-4-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylsulphonyl)thien-4-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thien-5-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxo-1,2,3,4-dihydroquinolin-6-ylthio)thien-4-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1,8-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thien-4-yl]tetrahydropyran, 4-[2-(8-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thien-4-yl]-4-hydroxy-2-methyltetrahydropyran, 4-[2-(7-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)thien-4-yl]-4-hydroxy-2-

methyltetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[2-(1-methyl-2-oxoindolin-5-ylthio)thien-4-yl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]tetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]tetrahydropyran, (2S,4R)-4-[3-(1-ethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]-4-hydroxy-2-methyltetrahydropyran, (2S,4R)-4-[3-(7-fluoro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]-4-hydroxy-2-methyltetrahydropyran, (2S,4R)-4-hydroxy-2-methyl-4-[3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-ylthio)phenyl]tetrahydropyran, (2S,4R)-4-[3-(8-chloro-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]-4-hydroxy-2-methyltetrahydropyran and (2S,4R)-4-hydroxy-2-methyl-4-[3-(1-methyl-2-oxoindolin-5-ylthio)phenyl]tetrahydropyran. See EP 623614 B1, incorporated herein by reference.

The compound can be represented by the formula:



wherein Q is a 10-membered bicyclic heterocyclic moiety containing one or two nitrogen heteroatoms which bears one or two thioxo substituents, and which heterocyclic moiety may optionally bear one, two or three further substituents selected from halogeno, hydroxy, cyano, amino, (1-4C)alkyl, (1-4C)alkoxy, fluoro-(1-4C)alkyl, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, phenyl and phenyl-(1-4C)alkyl, and wherein said phenyl or phenyl-(1-4C)alkyl substituent may optionally bear a substituent selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; wherein A is a direct link to X or is (1-3C)alkylene; wherein X is oxy, thio, sulphonyl, sulphonyl or imino; wherein Ar is phenylene which may optionally bear

one or two substituents selected from halogeno, hydroxy, amino, nitro, cyano, carbamoyl, ureido, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, fluoro-(1-4C)alkyl and (2-4C)alkanoylamino; or Ar is pyridylene; wherein R is (1-4C)alkyl, (3-4C)alkenyl or (3-4C)alkynyl; and wherein R and R

5 together form a group of the formula -A-X-A- which, together with the carbon atom to which A and A are attached, defines a ring having 5 to 7 ring atoms, wherein A and A, which may be the same or different, each is (1-3C)alkylene and X is oxy, thio, sulphinyl or sulphonyl, and which ring may bear one, two or three substituents, which may be the same or different, selected from hydroxy, (1-

10 4C)alkyl and (1-4C)alkoxy; or wherein R and R together form a group of the formula -A-X-A- which, together with the oxygen atom to which A is attached and with the carbon atom to which A is attached, defines a ring having 5 to 7 ring atoms, wherein A and A, which may be the same or different, each is (1-

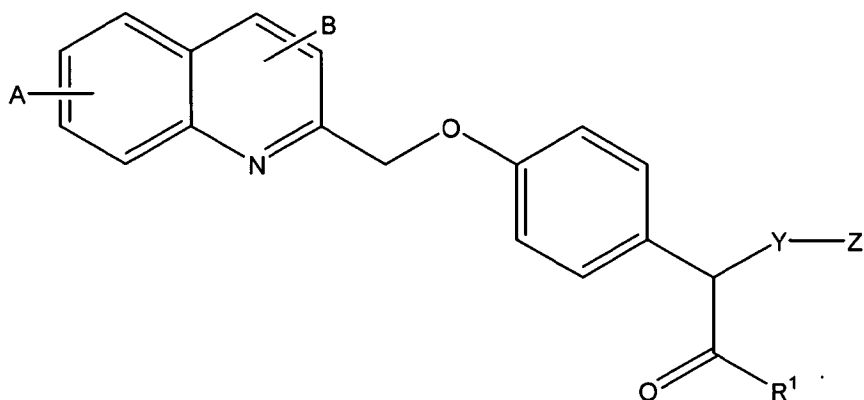
15 3C)alkylene and X is oxy, thio, sulphinyl or sulphonyl, and which ring may bear one, two or three (1-4C)alkyl substituents, and wherein R is (1-4C)alkyl, (2-4C)alkenyl or (2-4C)alkynyl; or a pharmaceutically-acceptable salt thereof. Preferably, the compound is selected from the group consisting of: 4-(5-fluoro-3-(1-methyl-2-thioxo-1,2-dihydroquinolin-6-ylmethoxy)phenyl]-4-

20 ethoxytetrahydropyran and 4-(5-fluoro-3-(1-methyl-2-thioxo-1,2,3,4-tetrahydroquinolin-6-ylmethoxy)phenyl]-4-methoxytetrahydropyran, 4-(5-fluoro-3-(1-methyl-2-thioxo-1,2,3,4-tetrahydroquinolin-6-ylthio)phenyl]-4-methoxytetrahydropyran and pharmaceutically-acceptable salt thereof. See EP 466452 B1, incorporated herein by reference.

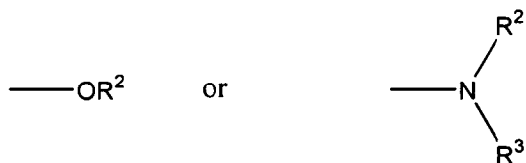
The compound can be a substituted 4-(quinolin-2-ylmethoxy)phenylacetic acid

25 derivative represented by the following formula:

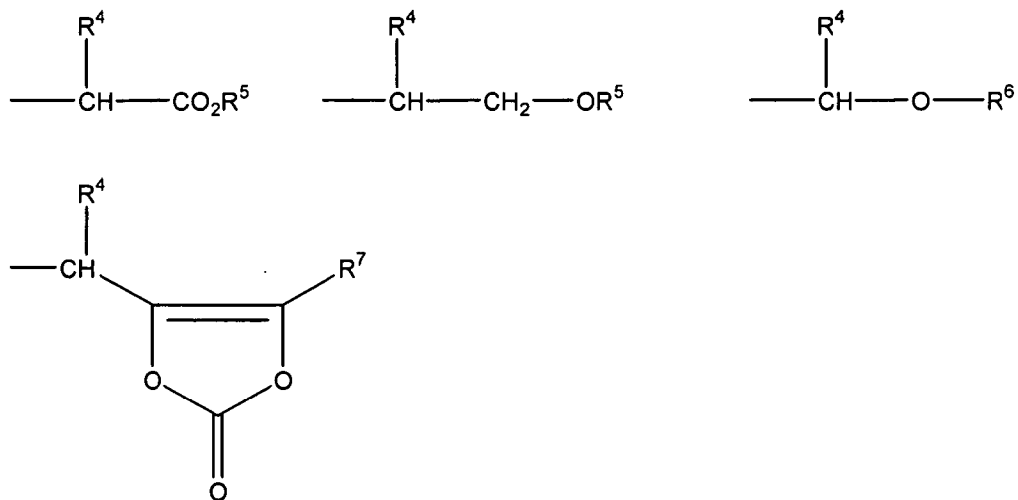
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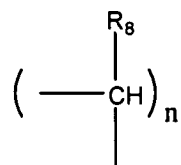
or pharmaceutically acceptable salt thereof, wherein R^1 represents a group of
 5 the formula:



R^2 and R^3 are identical or different and represent hydrogen, lower alkyl, phenyl,
 10 benzyl or a group of the formula:

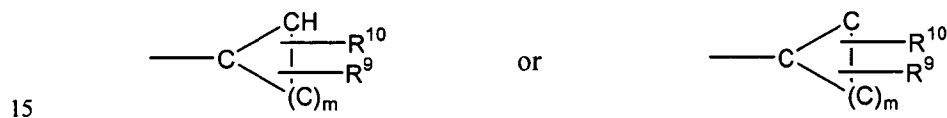


R⁴ represents hydrogen, lower alkyl, phenyl or benzyl, which can optionally be substituted by hydroxyl, carboxyl, lower alkoxy carbonyl, lower alkylthio,
 5 heteroaryl or carbamoyl, R⁵ represents hydrogen, lower alkyl, phenyl or benzyl, R⁶ represents a group of the formula -COR⁵ or -CO²R⁵, R⁷ represents hydrogen, lower alkyl or phenyl, Y represents a group of the formula:



10

wherein R⁸ represents hydrogen, lower alkyl or phenyl and n denotes a number of 0 to 5, Z represents norbornyl, or represents a group of the formula:

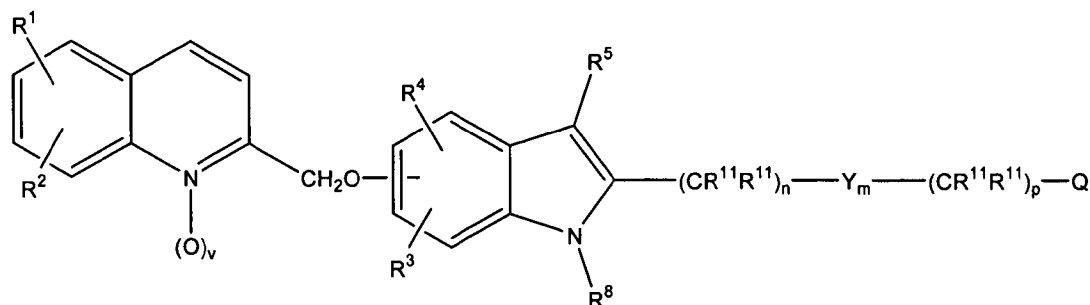


15

wherein R⁹ and R¹⁰ are identical or different and denote hydrogen, lower alkyl or phenyl, or R⁹ and R¹⁰ can together form a saturated carbocyclic ring having up to
 20 6 carbon atoms and m denotes a number from 1 to 6, and A and B are identical or different and denote hydrogen, lower alkyl or halogen, or a pharmaceutically acceptable salt thereof. Preferably the compounds are selected from the group consisting of: 2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclopentylacetic acid, 2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclohexylacetic acid, and 2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cycloheptylacetic acid, (+)-enantiomer of 2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclopentylacetic acid, (-)-enantiomer of 2-[4-(quinolin-2-yl-methoxy)phenyl]-2-cyclopentylacetic acid and pharmaceutically acceptable salts thereof. See U.S. Patent No. 4,970,215, incorporated herein by reference.

25

The compound can be represented by the formula:



5

wherein R, R, R, R and R are independently hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, -CF₃, -CN, -NO₂, -N₃, -C(OH)RR, -CO₂R, -SR, -S(O)R, -S(O)₂R, -S(O)₂NRR, -OR, -NRR, -C(O)R or -(CH₂)tR; R is hydrogen, -CH₃, -CF₃, -C(O)H, X-R or X-R; R and R are independently: alkyl, -(CH₂)uPh(R)₂ or -(CH₂)uTh(R)₂; R is -CF₃ or R; R is hydrogen or X-R; each R is independently hydrogen or lower alkyl, or two R's on same carbon atom are joined to form a cycloalkyl ring of 3 to 6 carbon atoms; R is hydrogen, lower alkyl or -CH₂R;

R is lower alkyl or -(CH₂)rR; R is -CF₃ or R; R is hydrogen, -C(O)R, R, or two R 's on the same nitrogen may be joined to form a monocyclic heterocyclic ring of 4 to 6 atoms containing up to 2 heteroatoms chosen from O, S or N; R is hydrogen, -CF₃, lower alkyl, lower alkenyl, lower alkynyl or -(CH₂)rR; R is -(CH₂)s-C(RR)-(CH₂)s-R or -CH₂C(O)NRR; R is hydrogen or lower alkyl; R is a) a monocyclic or bicyclic heterocyclic ring containing from 3 to 9 nuclear carbon atoms and 1 or 2 nuclear hetero-atoms selected from N, S or O and with each ring in the heterocyclic radical being formed of 5 or 6 atoms, or b) the radical W-R; R is alkyl or C(O)R; R is phenyl substituted with 1 or 2 R groups; R is hydrogen, halogen, lower alkyl, lower alkoxy, lower alkylthio, lower alkylsulfonyl, lower alkylcarbonyl, -CF₃, -CN, -NO₂ or -N₃; R is alkyl, cycloalkyl, monocyclic monoheterocyclic ring; R is the residual structure of a standard amino acid, or R and R attached to the same

N can cyclize to form a proline residue; m is 0 to 1; n is 0 to 3; p is 1 to 3 when m is 1; p is 0 to 3 when m is 0; r is 0 to 2; s is 0 to 3; t is 0 to 2; u is 0 to 3; v is 0 or 1; W is 0, S or NR; X is 0, or NR; X is C(O), CRR, S, S(O) or S(O)₂; X is C(O), CRR, S(O)₂ or a bond; Y is X or X; Q is -CO₂R, -C(O)NHS(O)₂R, -NHS(O)₂R, -S(O)₂NHR -C(O)NRR, -CO₂R, -C(O)NRR, -CH₂OH, or 1H- or 2H-tetrazol-5-yl; and the pharmaceutically acceptable salts thereof. Preferred embodiments of the compounds are selected from the following and pharmaceutically acceptable salts thereof:

- 10 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-methyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-t-butylthiobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 15 3-[N-(p-chlorobenzyl)-3-(phenylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-(phenylsulfonyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethyl propanoic acid, N-oxide;
- 20 3-[N-(p-chlorobenzyl)-3-(phenylsulfonyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-(phenylsulfinyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;;
- 25 3-[N-(p-chlorobenzyl)-3-benzoyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-benzyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 30 3-[N-(p-chlorobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 2-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-

- yl]ethoxyethanoic acid;
- 3-[N-(p-chlorobenzyl)-3-(3,3-dimethyl-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2-methylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-methyl-5-(6,7-dichloroquinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-3-methyl-5-(7-chloroquinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-4-allyl-5-(quinolin-2-ylmethoxy)-3-(t-butylthio)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-4-allyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-6-(quinolin-2-ylmethoxy)-3-(t-butylthio)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-4-(quinolin-2-ylmethoxy)-3-(t-butylthio)indol-2-yl]-2,2-dimethylpropanoic acid;
- 3-[N-(p-chlorobenzyl)-7-(quinolin-2-ylmethoxy)-3-(t-butylthio)indol-2-yl]-2,2-dimethylpropanoic acid;
- 2-[2-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]ethoxy]propanoic acid;
- 3-[N-(p-chlorobenzyl)-4-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid;;
- 3-[N-methyl-3-(p-chlorobenzoyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
- 3-[N-methyl-3-(p-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
- 3-[N-(4-chlorobenzyl)-3-i-propoxy-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
- 3-[N-(4-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2-ethylpropanoic acid,
- 3-[N-(4-chlorobenzyl)-3-trifluoroacetyl-5-(quinolin-2-ylmethoxy)indol-

- 2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(4-chlorobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2-methylpropanoic acid,
 3-[3-(3,3-dimethyl-1-oxo-1-butyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-
 5 2,2-dimethylpropanoic acid,
 3-[N-(4-trifluoromethylbenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-yl-methoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-benzyl-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 10 3-[N-(3-methoxybenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-allyl-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(4-methoxybenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 15 3-[N-methyl-3-(3,3-dimethyl-1-oxo-3-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid.
 20 3-[N-(phenylsulfonyl)-3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-benzyl-3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(4-chlorobenzyl)-3-(t-butylsulfonyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 25 3-[N-(4-chlorobenzyl)-3-(t-butylsulfinyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-allyl-3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 30 3-[N-(n-propyl)-3-(4-chlorobenzyl)-6-(quinoline-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-ethyl-3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-

- dimethylpropanoic acid,
3-[N-(4-chlorobenzyl)-3-(4-t-butylbenzoyl)-5-(quinolin-2-yl-
methoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
3-[N-(4-chlorobenzyl)-3-(4-chlorobenzoyl)-5-(quinolin-2-
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
5 3-[N-(4-chlorobenzyl)-3-(1,1-dimethylethyl)-5-(quinolin-2-
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
3-[N-(4-chlorobenzyl)-3-acetyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-
2,2-dimethylpropanoic acid
10 3-[N-(4-chlorobenzyl)-3-cyclopropanecarbonyl-5-(quinolin-2-
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
3-[N-(4-chlorobenzyl)-3-(3-cyclopentylpropanoyl)-5-(quinolin-2-
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
3-[N-(4-chlorobenzyl)-3-(3-methylbutanoyl)-5-(quinolin-2-yl-
methoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
15 3-[N-(4-chlorobenzyl)-3-propanoyl-5-(quinolin-2-ylmethoxy)indol-2-
yl]-2,2-dimethylpropanoic acid,
3-[N-(4-chlorobenzyl)-3-(2-methylpropanoyl)-5-(quinolin-2-
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
20 3-[N-(4-chlorobenzyl)-3-trimethylacetyl-5-(quinolin-2-ylmethoxy)indol-
2-yl]-2,2-dimethylpropanoic acid,
3-[N-(4-chlorobenzyl)-3-phenylacetyl-5-(quinolin-2-ylmethoxy)indol-2-
yl]-2,2-dimethylpropanoic acid,
3-[N-(4-fluorobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
25 3-[N-(4-bromobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
3-[N-(4-iodobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
30 3-[N-(4-chlorobenzyl)-3-(1,1-dimethylbutyl)-5-(quinolin-2-
ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
3-[N-(4-chlorobenzyl)-3-(1,1-dimethylpropyl)-5-(quinolin-2-

- ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(3-fluorobenzyl)-3-(1,1-dimethylethyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(4-chlorobenzyl)-3-(3-methylethyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 5 3-[N-(4-chlorobenzyl)-3-cyclopropyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(4-chlorobenzyl)-3-(1-methyl-1-cyclopropyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 10 3-[N-(4-chlorobenzyl)-3-cyclopentyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(4-chlorobenzyl)-3-cyclohexyl-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(4-chlorobenzyl)-3-(α , α -dimethylbenzyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 15 3-[N-(4-chlorobenzyl)-3-(2-{4-chloro- α , α -dimethylbenzyl})-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(4-chlorobenzyl)-3-(1-adamantyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 20 3-[N-(4-chlorobenzyl)-3-((1-adamantyl)methyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(1,1-dimethylethyl)-3-(4-chlorobenzyl)-6-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 3-[N-(1,1-dimethylpropyl)-3-(4-chlorobenzyl)-6-(quinoline-2-ylmethoxy)indol-2-yl]-2,2-dimethylpropanoic acid,
 25 3-[N-(4-chlorobenzyl)-3-(3,3-dimethyl-1-oxo-1-butyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-diethylpropanoic acid,
 methyl 3-[N-(4-chlorobenzyl)-3,6-bis(acetyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2 dimethyl propanoate or
 30 methyl 3-[N-(4-chlorobenzyl)-3,6-bis(cyclopropanecarbonyl)-5-(quinolin-2-ylmethoxy)indol-2-yl]-2,2-dimethyl propanoate. See EP 419049 B1, incorporated herein by reference.

The term "alkyl" refers to a monovalent group derived from a straight or branched chain saturated hydrocarbon by the removal of a single hydrogen atom. Alkyl groups are exemplified by methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl, and the like. The term "hydroxyalkyl" represents an alkyl group, as defined above, substituted by one to three hydroxyl groups with the proviso that no more than one hydroxy group may be attached to a single carbon atom of the alkyl group. The term "alkylamino" refers to a group having the structure -NHR' wherein R' is alkyl, as previously defined, examples of alkylamino include methylamino, ethylamino, iso-propylamino and the like.

The term "alkylaminocarbonyl" refers to an alkylamino group, as previously defined, attached to the parent molecular moiety through a carbonyl group. Examples of alkylaminocarbonyl include methylamino-carbonyl, ethylaminocarbonyl, iso-propylaminocarbonyl and the like. The term "alkylthio" refers to an alkyl group, as defined above, attached to the parent molecular moiety through a sulfur atom and includes such examples as methylthio, ethylthio, propylthio, n-, sec- and tert-butylthio and the like. The term "alkanoyl" represents an alkyl group, as defined above, attached to the parent molecular moiety through a carbonyl group. Alkanoyl groups are exemplified by formyl, acetyl, propionyl, butanoyl and the like. The term "alkanoylamino" refers to an alkanoyl group, as previously defined, attached to the parent molecular moiety through a nitrogen atom. Examples of alkanoylamino include formamido, acetamido, and the like. The term "N-alkanoyl-N-alkylamino" refers to an alkanoyl group, as previously defined, attached to the parent molecular moiety through an aminoalkyl group. Examples of N-alkanoyl-N-alkylamino include N-methylformamido, N-methyl-acetamido, and the like. The terms "alkoxy" or "alkoxyl" denote an alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom. Representative alkoxy groups include methoxyl, ethoxyl, propoxyl, butoxyl, and the like. The term "alkoxyalkoxyl" refers to an alkyl group, as defined above, attached through an oxygen to an alkyl group, as defined above, attached in turn through an oxygen to the parent molecular moiety. Examples of alkoxyalkoxyl include methoxymethoxyl, methoxyethoxyl, ethoxyethoxyl and the like. The

term "alkoxyalkyl" refers to an alkoxy group, as defined above, attached through an alkylene group to the parent molecular moiety. The term "alkoxycarbonyl" represents an ester group; *i.e.*, an alkoxy group, attached to the parent molecular moiety through a carbonyl group such as

5 methoxycarbonyl, ethoxycarbonyl, and the like. The term "alkenyl" denotes a monovalent group derived from a hydrocarbon containing at least one carbon-carbon double bond by the removal of a single hydrogen atom. Alkenyl groups include, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl and the like. The term "alkylene" denotes a divalent group derived from a straight or

10 branched chain saturated hydrocarbon by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-dimethylpropylene, and the like. The term "alkenylene" denotes a divalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond. Examples of alkenylene include $-\text{CH}=\text{CH}-$, $-\text{CH}_2\text{CH}=\text{CH}-$,

15 $-\text{C}(\text{CH}_3)=\text{CH}-$, $-\text{CH}_2\text{CH}=\text{CHCH}_2-$, and the like. The term "cycloalkylene" refers to a divalent group derived from a saturated carbocyclic hydrocarbon by the removal of two hydrogen atoms, for example cyclopentylene, cyclohexylene, and the like. The term "cycloalkyl" denotes a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptanyl, and bicyclo[2.2.2]octanyl. The term "alkynylene" refers to a divalent group derived by the removal of two hydrogen atoms from a straight or branched chain acyclic hydrocarbon group containing a carbon-carbon triple bond. Examples of

25 alkynylene include $-\text{CH}\equiv\text{CH}-$, $-\text{CH}\equiv\text{CH}-\text{CH}_2-$, $-\text{CH}\equiv\text{CH}-\text{CH}(\text{CH}_3)-$, and the like. The term "carbocyclic aryl" denotes a monovalent carbocyclic ring group derived by the removal of a single hydrogen atom from a monocyclic or bicyclic fused or non-fused ring system obeying the " $4n+2$ p electron" or Huckel aromaticity rule. Examples of carbocyclic aryl groups include phenyl,

30 1- and 2-naphthyl, biphenyl, fluorenyl, and the like. The term "(carbocyclic aryl)alkyl" refers to a carbocyclic aryl ring group as defined above, attached to the parent molecular moiety through an alkylene group. Representative

(carbocyclic aryl)alkyl groups include phenylmethyl, phenylethyl, phenylpropyl, 1-naphthylmethyl, and the like. The term "carbocyclicarylalkoxy" refers to a carbocyclicaryl alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom. The term "carbocyclic

5 aryloxyalkyl" refers to a carbocyclic aryl group, as defined above, attached to the parent molecular moiety through an oxygen atom and thence through an alkylene group. Such groups are exemplified by phenoxymethyl, 1- and 2-naphthylloxymethyl, phenoxyethyl and the like. The term "(carbocyclic aryl)alkoxyalkyl" denotes a carbocyclic aryl group as defined above, attached to

10 the parent molecular moiety through an alkoxyalkyl group. Representative (carbocyclic aryl)alkoxyalkyl groups include phenylmethoxymethyl, phenylethoxymethyl, 1- and 2-naphthylmethoxyethyl, and the like. "Carbocyclic arylthioalkyl" represents a carbocyclic aryl group as defined above, attached to the parent molecular moiety through a sulfur atom and thence

15 through an alkylene group and are typified by phenylthiomethyl, 1- and 2-naphthylthioethyl and the like. The term "dialkylamino" refers to a group having the structure $-NR'R''$ wherein R' and R'' are independently selected from alkyl, as previously defined. Additionally, R' and R'' taken together may optionally be $-(CH_2)_{kk}$ -- where kk is an integer of from 2 to 6. Examples of

20 dialkylamino include, dimethylamino, diethylaminocarbonyl, methylethylamino, piperidino, and the like. The term "halo or halogen" denotes fluorine, chlorine, bromine or iodine. The term "haloalkyl" denotes an alkyl group, as defined above, having one, two, or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl,

25 trifluoromethyl, and the like. The term "hydroxyalkyl" represents an alkyl group, as defined above, substituted by one to three hydroxyl groups with the proviso that no more than one hydroxy group may be attached to a single carbon atom of the alkyl group. The term "phenoxy" refers to a phenyl group attached to the parent molecular moiety through an oxygen atom. The term "phenylthio"

30 refers to a phenyl group attached to the parent molecular moiety through a sulfur atom. The term "pyridyloxy" refers to a pyridyl group attached to the parent molecular moiety through an oxygen atom. The terms "heteroaryl" or

"heterocyclic aryl" as used herein refers to substituted or unsubstituted 5- or 6-membered ring aromatic groups containing one oxygen atom, one, two, three, or four nitrogen atoms, one nitrogen and one sulfur atom, or one nitrogen and one oxygen atom. The term heteroaryl also includes bi- or tricyclic groups in which the aromatic heterocyclic ring is fused to one or two benzene rings.

Representative heteroaryl groups are pyridyl, thienyl, indolyl, pyrazinyl, isoquinolyl, pyrrolyl, pyrimidyl, benzothienyl, furyl, benzo[b]furyl, imidazolyl, thiazolyl, carbazolyl, and the like. The term "heteroarylalkyl" denotes a heteroaryl group, as defined above, attached to the parent molecular moiety through an alkylene group. The term "heteroaryloxy" denotes a heteroaryl group, as defined above, attached to the parent molecular moiety through an oxygen atom. The term "heteroarylalkoxy" denotes a heteroarylalkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom.

NUCLEIC ACID THERAPEUTIC AGENTS

In another embodiment, a nucleic acid of the invention; a nucleic acid complementary to a nucleic acid of the invention; or a portion of such a nucleic acid (*e.g.*, an oligonucleotide as described below); or a nucleic acid encoding a member of the leukotriene pathway (*e.g.*, 5-LO), can be used in "antisense" therapy, in which a nucleic acid (*e.g.*, an oligonucleotide) which specifically hybridizes to the mRNA and/or genomic DNA of a nucleic acid is administered or generated *in situ*. The antisense nucleic acid that specifically hybridizes to the mRNA and/or DNA inhibits expression of the polypeptide encoded by that mRNA and/or DNA, *e.g.*, by inhibiting translation and/or transcription. Binding of the antisense nucleic acid can be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interaction in the major groove of the double helix.

An antisense construct can be delivered, for example, as an expression plasmid as described above. When the plasmid is transcribed in the cell, it produces RNA that is complementary to a portion of the mRNA and/or DNA that encodes the polypeptide for the member of the leukotriene pathway (*e.g.*,

FLAP or 5-LO). Alternatively, the antisense construct can be an oligonucleotide probe that is generated *ex vivo* and introduced into cells; it then inhibits expression by hybridizing with the mRNA and/or genomic DNA of the polypeptide. In one embodiment, the oligonucleotide probes are modified
5 oligonucleotides that are resistant to endogenous nucleases, *e.g.*, exonucleases and/or endonucleases, thereby rendering them stable *in vivo*. Exemplary nucleic acid molecules for use as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Pat. Nos. 5,176,996, 5,264,564 and 5,256,775). Additionally, general approaches to
10 constructing oligomers useful in antisense therapy are also described, for example, by Van der Krol *et al.* (*Biotechniques* 6:958-976 (1988)); and Stein *et al.* (*Cancer Res.* 48:2659-2668 (1988)). With respect to antisense DNA, oligodeoxyribonucleotides derived from the translation initiation site are preferred.

15 To perform antisense therapy, oligonucleotides (mRNA, cDNA or DNA) are designed that are complementary to mRNA encoding the polypeptide. The antisense oligonucleotides bind to mRNA transcripts and prevent translation. Absolute complementarity, although preferred, is not required. A sequence "complementary" to a portion of an RNA, as referred to
20 herein, indicates that a sequence has sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid,
25 as described in detail above. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures.

30 The oligonucleotides used in antisense therapy can be DNA, RNA, or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotides can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the

molecule, hybridization, etc. The oligonucleotides can include other appended groups such as peptides (*e.g.* for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA* 86:6553-6556 (1989); Lemaitre *et al.*, *Proc. Natl. Acad. Sci. USA* 84:648-652 (1987); PCT International Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT International Publication No. WO 89/10134), or hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, *BioTechniques* 6:958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, *Pharm.Res.* 5: 539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent).

The antisense molecules are delivered to cells that express the member of the leukotriene pathway *in vivo*. A number of methods can be used for delivering antisense DNA or RNA to cells; *e.g.*, antisense molecules can be injected directly into the tissue site, or modified antisense molecules, designed to target the desired cells (*e.g.*, antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systematically. Alternatively, in a preferred embodiment, a recombinant DNA construct is utilized in which the antisense oligonucleotide is placed under the control of a strong promoter (*e.g.*, pol III or pol II). The use of such a construct to transfect target cells in the patient results in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous transcripts and thereby prevent translation of the mRNA. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art and described above. For example, a plasmid, cosmid, YAC or viral vector can be used to prepare the recombinant DNA construct that can be introduced directly into the tissue site. Alternatively, viral vectors can be used which selectively

infect the desired tissue, in which case administration may be accomplished by another route (*e.g.*, systemically).

In another embodiment of the invention, small double-stranded interfering RNA (RNA interference (RNAi)) can be used. RNAi is a post-transcription process, in which double-stranded RNA is introduced, and sequence-specific gene silencing results, though catalytic degradation of the targeted mRNA. See, *e.g.*, Elbashir, S.M. *et al.*, *Nature* 411:494-498 (2001); Lee, N.S., *Nature Biotech.* 19:500-505 (2002); Lee, S-K. *et al.*, *Nature Medicine* 8(7):681-686 (2002); the entire teachings of these references are incorporated herein by reference. RNAi is used routinely to investigate gene function in a high throughput fashion or to modulate gene expression in human diseases (Chi *et al.*, *PNAS*, 100 (11):6343-6346 (2003)). Introduction of long double stranded RNA leads to sequence-specific degradation of homologous gene transcripts. The long double stranded RNA is metabolized to small 21-23 nucleotide siRNA (small interfering RNA). The siRNA then binds to protein complex RISC (RNA-induced silencing complex) with dual function helicase. The helicase has RNase activity and is able to unwind the RNA. The unwound siRNA allows an antisense strand to bind to a target. This results in sequence dependent degradation of cognate mRNA. Aside from endogenous RNAi, exogenous RNAi, chemically synthesized or recombinantly produced can also be used. Using non-intronic portions of the FLAP gene, such as corresponding mRNA portions of SEQ ID NO.1, or portions of SEQ ID NO: 3, target regions of the FLAP gene that are accessible for RNAi are targeted and silenced. With this technique it is possible to conduct a RNAi gene walk of the nucleic acids of the FLAP gene and determine the amount of inhibition of the protein product. Thus it is possible to design gene-specific therapeutics by directly targeting the mRNAs of the gene.

Endogenous expression of a member of the leukotriene pathway (*e.g.*, FLAP, 5-LO) can also be reduced by inactivating or “knocking out” the gene or its promoter using targeted homologous recombination (*e.g.*, see Smithies *et al.*, *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson *et al.*, *Cell* 5:313-321 (1989)). For example, an altered, non-

functional gene of a member of the leukotriene pathway (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous gene (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect
5 cells that express the gene *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the gene. The recombinant DNA constructs can be directly administered or targeted to the required site *in vivo* using appropriate vectors, as described above. Alternatively, expression of non-altered genes can be increased using a similar
10 method: targeted homologous recombination can be used to insert a DNA construct comprising a non-altered functional gene, or the complement thereof, or a portion thereof, in place of an gene in the cell, as described above. In another embodiment, targeted homologous recombination can be used to insert a DNA construct comprising a nucleic acid that encodes a polypeptide variant
15 that differs from that present in the cell.

Alternatively, endogenous expression of a member of the leukotriene pathway can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of the member of the leukotriene pathway (*i.e.*, the promoter and/or enhancers) to form triple helical structures
20 that prevent transcription of the gene in target cells in the body. (See generally, Helene, C., *Anticancer Drug Des.*, 6(6):569-84 (1991); Helene, C. *et al.*, *Ann. N.Y. Acad. Sci.* 660:27-36 (1992); and Maher, L. J., *Bioassays* 14(12):807-15 (1992)). Likewise, the antisense constructs described herein, by antagonizing the normal biological activity of one of the members of the leukotriene
25 pathway, can be used in the manipulation of tissue, *e.g.*, tissue differentiation, both *in vivo* and *for ex vivo* tissue cultures. Furthermore, the anti-sense techniques (*e.g.*, microinjection of antisense molecules, or transfection with plasmids whose transcripts are anti-sense with regard to a nucleic acid RNA or nucleic acid sequence) can be used to investigate the role of one or more
30 members of the leukotriene pathway in the development of disease-related conditions. Such techniques can be utilized in cell culture, but can also be used in the creation of transgenic animals.

The therapeutic agents as described herein can be delivered in a composition, as described above, or by themselves. They can be administered systemically, or can be targeted to a particular tissue. The therapeutic agents can be produced by a variety of means, including chemical synthesis; 5 recombinant production; *in vivo* production (*e.g.*, a transgenic animal, such as U.S. Pat. No. 4,873,316 to Meade *et al.*), for example, and can be isolated using standard means such as those described herein. In addition, a combination of any of the above methods of treatment (*e.g.*, administration of non-altered polypeptide in conjunction with antisense therapy targeting altered mRNA for a 10 member of the leukotriene pathway; administration of a first splicing variant in conjunction with antisense therapy targeting a second splicing variant) can also be used.

The invention additionally pertains to use of such therapeutic agents, as described herein, for the manufacture of a medicament for the treatment of MI, 15 ACS, stroke, PAOD and/or atherosclerosis, *e.g.*, using the methods described herein.

MONITORING PROGRESS OF TREATMENT

The current invention also pertains to methods of monitoring the 20 response of an individual, such as an individual in one of the target populations described above, to treatment with a leukotriene synthesis inhibitor.

Because the level of inflammatory markers can be elevated in individuals who are in the target populations described above, an assessment of the level of inflammatory markers of the individual both before, and during, 25 treatment with the leukotriene synthesis inhibitor will indicate whether the treatment has successfully decreased production of leukotrienes in the arterial vessel wall or in bone-marrow derived inflammatory cells. For example, in one embodiment of the invention, an individual who is a member of a target population as described above (*e.g.*, an individual at risk for MI, ACS, stroke or 30 PAOD, such as an individual who is at-risk due to a FLAP haplotype) can be assessed for response to treatment with a leukotriene synthesis inhibitor, by examining leukotriene levels or leukotriene metabolite levels in the individual.

Blood, serum, plasma or urinary leukotrienes (*e.g.*, leukotriene E4, cysteinyl leukotriene 1), or *ex vivo* production of leukotrienes (*e.g.*, in blood samples stimulated with a calcium ionophore to produce leukotrienes), or leukotriene metabolites, can be measured before, and during or after treatment with the leukotriene synthesis inhibitor. The leukotriene or leukotriene metabolite level before treatment is compared with the leukotriene or leukotriene metabolite level during or after treatment. The efficacy of treatment is indicated by a decrease in leukotriene production: a level of leukotriene or leukotriene metabolite during or after treatment that is significantly lower than the level of leukotriene or leukotriene metabolite before treatment, is indicative of efficacy. A level that is lower during or after treatment can be shown, for example, by decreased serum or urinary leukotrienes, or decreased *ex vivo* production of leukotrienes, or decreased leukotriene metabolites. A level that is “significantly lower”, as used herein, is a level that is less than the amount that is typically found in control individual(s), or is less in a comparison of disease risk in a population associated with the other bands of measurement (*e.g.*, the mean or median, the highest quartile or the highest quintile) compared to lower bands of measurement (*e.g.*, the mean or median, the other quartiles; the other quintiles).

For example, in one embodiment of the invention, the level of a leukotriene or leukotriene metabolite is assessed in an individual before treatment with a leukotriene synthesis inhibitor; and during or after treatment with the leukotriene synthesis inhibitor, and the levels are compared. A level of the leukotriene or leukotriene metabolite during or after treatment that is significantly lower than the level of the leukotriene or leukotriene metabolite before treatment, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor. In another embodiment, production of a leukotriene or a leukotriene metabolite is stimulated in a first test sample from the individual, using a calcium ionophore, before treatment with a leukotriene synthesis inhibitor, and is also stimulated in a second test sample from the individual, using a calcium ionophore, during or after treatment with the leukotriene synthesis inhibitor, and the level of production in the first test sample is compared with the level of production of the leukotriene or leukotriene

metabolite in the second test sample. A level of the leukotriene or leukotriene metabolite in the second test sample that is significantly lower than the level of the leukotriene or leukotriene metabolite in the first test sample, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor.

5 In another embodiment of the invention, an individual who is a member of a target population of individuals at risk for MI, ACS, stroke or PAOD (*e.g.*, an individual in a target population described above, such as an individual at-risk due to elevated C-reactive protein) can be assessed for response to treatment with a leukotriene synthesis inhibitor, by examining levels of
10 inflammatory markers in the individual. For example, levels of an inflammatory marker in an appropriate test sample (*e.g.*, serum, plasma or urine) can be measured before, and during or after treatment with the leukotriene synthesis inhibitor. The level of the inflammatory marker before treatment is compared with the level of the inflammatory marker during or after
15 treatment. The efficacy of treatment is indicated by a decrease in the level of the inflammatory marker, that is, a level of the inflammatory marker during or after treatment that is significantly lower (*e.g.*, significantly lower), than the level of inflammatory marker before treatment, is indicative of efficacy. Representative inflammatory markers include: C-reactive protein (CRP), serum
20 amyloid A, fibrinogen, a leukotriene (*e.g.*, LTB₄, LTC₄, LTD₄, LTE₄), a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease
25 type-9, myeloperoxidase (MPO), and N-tyrosine. In a preferred embodiment, the marker is CRP or MPO.

ASSESSMENT OF INCREASED RISK

30 The present invention additionally pertains to methods for assessing an individual (*e.g.*, an individual who is in a target population as described herein, such as an individual who is at risk for MI, ACS, stroke or PAOD), for an increased risk of MI, ACS, atherosclerosis, stroke, transient ischemic attack, transient monocular blindness, asymptomatic carotid stenosis, PAOD,

claudication, or limb ischemia. The methods comprise assessing the level of a leukotriene metabolite (*e.g.*, LTE4, LTD4, LTB4) in the individual, wherein an increased level of leukotriene metabolite is indicative of an increased risk. The level can be measured in any appropriate tissue or fluid sample, such as blood, serum, plasma, or urine. In one particular embodiment, the sample comprises neutrophils. The level of the leukotriene metabolite can be measured by standard methods, such as the methods described herein. For example, in one embodiment, production of a leukotriene metabolite is stimulated in a first test sample from the individual, using a calcium ionophore. The level of production is compared with a control level. The control level is a level that is typically found in control individual(s), such as individual who are not at risk for MI, ACS, stroke or PAOD; alternatively, a control level is the level that is found by comparison of disease risk in a population associated with the lowest band of measurement (*e.g.*, below the mean or median, the lowest quartile or the lowest quintile) compared to higher bands of measurement (*e.g.*, above the mean or median, the second, third or fourth quartile; the second, third, fourth or fifth quintile). A level of production of the leukotriene metabolite that is significantly greater than the control level, is indicative of an increased risk. Individuals at increased risk are candidates for treatments described herein.

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PHARMACEUTICAL COMPOSITIONS

The present invention also pertains to pharmaceutical compositions comprising agents described herein, for example, an agent that is a leukotriene synthesis inhibitor as described herein. For instance, a leukotriene synthesis inhibitor can be formulated with a physiologically acceptable carrier or excipient to prepare a pharmaceutical composition. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (*e.g.*, NaCl), saline, buffered saline, alcohols, glycerol, ethanol, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols,

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gelatin, carbohydrates such as lactose, amylose or starch, dextrose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, etc., as well as combinations thereof. The pharmaceutical preparations can, if desired, be mixed with
5 auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active agents.

The composition, if desired, can also contain minor amounts of wetting
10 or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose,
15 starch, magnesium stearate, polyvinyl pyrrolidone, sodium saccharine, cellulose, magnesium carbonate, etc.

Methods of introduction of these compositions include, but are not limited to, intradermal, intramuscular, intraperitoneal, intraocular, intravenous, subcutaneous, topical, oral and intranasal. Other suitable methods of
20 introduction can also include gene therapy (as described below), rechargeable or biodegradable devices, particle acceleration devices ("gene guns") and slow release polymeric devices. The pharmaceutical compositions of this invention can also be administered as part of a combinatorial therapy with other agents.

The composition can be formulated in accordance with the routine
25 procedures as a pharmaceutical composition adapted for administration to human beings. For example, compositions for intravenous administration typically are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either
30 separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the

composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients
5 may be mixed prior to administration.

For topical application, nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water, can be employed. Suitable formulations include but are not limited to solutions, suspensions, emulsions,
10 creams, ointments, powders, enemas, lotions, sols, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, *e.g.*, preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The agent may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the
15 active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, *e.g.*, pressurized air.

Agents described herein can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups
20 such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The agents are administered in a therapeutically effective amount. The
25 amount of agents which will be therapeutically effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also
30 depend on the route of administration, and the seriousness of the symptoms, and should be decided according to the judgment of a practitioner and each patient's

circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (*e.g.*, separately, sequentially or concurrently), or the like. The pack or kit may also include means for reminding the patient to take the therapy. The pack or kit can be a single unit dosage of the combination therapy or it can be a plurality of unit dosages. In particular, the agents can be separated, mixed together in any combination, present in a single vial or tablet. Agents assembled in a blister pack or other dispensing means is preferred. For the purpose of this invention, unit dosage is intended to mean a dosage that is dependent on the individual pharmacodynamics of each agent and administered in FDA approved dosages in standard time courses.

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NUCLEIC ACIDS OF THE INVENTION

FLAP Nucleic Acids, Portions and Variants

In addition, the invention pertains to isolated nucleic acid molecules comprising a human FLAP nucleic acid. The term, "FLAP nucleic acid," as used herein, refers to an isolated nucleic acid molecule encoding FLAP polypeptide. The FLAP nucleic acid molecules of the present invention can be RNA, for example, mRNA, or DNA, such as cDNA and genomic DNA. DNA molecules can be double-stranded or single-stranded; single stranded RNA or DNA can be either the coding, or sense strand or the non-coding, or antisense strand. The nucleic acid molecule can include all or a portion of the coding sequence of the gene or nucleic acid and can further comprise additional non-

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coding sequences such as introns and non-coding 3' and 5' sequences (including regulatory sequences, for example, as well as promoters, transcription enhancement elements, splice donor/acceptor sites, etc.).

For example, a FLAP nucleic acid can consist of SEQ ID NOs: 1 or 3 or the complement thereof, or to a portion or fragment of such an isolated nucleic acid molecule (*e.g.*, cDNA or the nucleic acid) that encodes FLAP polypeptide (*e.g.*, a polypeptide such as SEQ ID NO: 2). In a preferred embodiment, the isolated nucleic acid molecule comprises a nucleic acid molecule selected from the group consisting of SEQ ID NOs: 1 or 3, or their complement thereof.

Additionally, the nucleic acid molecules of the invention can be fused to a marker sequence, for example, a sequence that encodes a polypeptide to assist in isolation or purification of the polypeptide. Such sequences include, but are not limited to, those that encode a glutathione-S-transferase (GST) fusion protein and those that encode a hemagglutinin A (HA) polypeptide marker from influenza.

An "isolated" nucleic acid molecule, as used herein, is one that is separated from nucleic acids that normally flank the gene or nucleic acid sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (*e.g.*, as in an RNA library). For example, an isolated nucleic acid of the invention may be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material will form part of a composition (for example, a crude extract containing other substances), buffer system or reagent mix. In other circumstances, the material may be purified to essential homogeneity, for example as determined by PAGE or column chromatography such as HPLC. In certain embodiments, an isolated nucleic acid molecule comprises at least about 50, 80 or 90% (on a molar basis) of all macromolecular species present. With regard to genomic DNA, the term "isolated" also can refer to nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule

can contain less than about 5 kb, including but not limited to 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotides which flank the nucleic acid molecule in the genomic DNA of the cell from which the nucleic acid molecule is derived.

5 The nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. Thus, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells, as well as partially or substantially purified DNA molecules in solution. "Isolated" nucleic acid molecules also encompass *in vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention. 10 An isolated nucleic acid molecule or nucleic acid sequence can include a nucleic acid molecule or nucleic acid sequence that is synthesized chemically or by recombinant means. Therefore, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleotide sequences include recombinant DNA molecules in heterologous organisms, as well as partially or substantially purified DNA molecules in solution. *In vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention are also encompassed by "isolated" nucleotide sequences. Such isolated nucleotide sequences are useful in the manufacture of the encoded polypeptide, as probes 15 for isolating homologous sequences (*e.g.*, from other mammalian species), for gene mapping (*e.g.*, by *in situ* hybridization with chromosomes), or for detecting expression of the nucleic acid in tissue (*e.g.*, human tissue), such as by Northern blot analysis. 20

The present invention also pertains to nucleic acid molecules which are not necessarily found in nature but which encode a FLAP polypeptide (*e.g.*, a 25 polypeptide having an amino acid sequence comprising an amino acid sequence of SEQ ID NOs: 2), or another splicing variant of a FLAP polypeptide or polymorphic variant thereof. Thus, for example, DNA molecules that comprise a sequence that is different from the naturally occurring nucleic acid sequence but which, due to the degeneracy of the genetic code, encode a FLAP polypeptide of the present invention are also the 30 subjects of this invention. The invention also encompasses nucleotide

sequences encoding portions (fragments), or encoding variant polypeptides such as analogues or derivatives of a FLAP polypeptide. Such variants can be naturally occurring, such as in the case of allelic variation or single nucleotide polymorphisms, or non-naturally-occurring, such as those induced by various mutagens and mutagenic processes. Intended variations include, but are not limited to, addition, deletion and substitution of one or more nucleotides that can result in conservative or non-conservative amino acid changes, including additions and deletions. Preferably the nucleotide (and/or resultant amino acid) changes are silent or conserved; that is, they do not alter the characteristics or activity of a FLAP polypeptide. In one preferred embodiment, the nucleotide sequences are fragments that comprise one or more polymorphic microsatellite markers. In another preferred embodiment, the nucleotide sequences are fragments that comprise one or more single nucleotide polymorphisms in a FLAP nucleic acid (*e.g.*, the single nucleotide polymorphisms set forth in Table 13, below).

Other alterations of the nucleic acid molecules of the invention can include, for example, labeling, methylation, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, carbamates), charged linkages (*e.g.*, phosphorothioates, phosphorodithioates), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine, psoralen), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids). Also included are synthetic molecules that mimic nucleic acid molecules in the ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The invention also pertains to nucleic acid molecules that hybridize under high stringency hybridization conditions, such as for selective hybridization, to a nucleic acid sequence described herein (*e.g.*, nucleic acid molecules which specifically hybridize to a nucleic acid sequence encoding polypeptides described herein, and, optionally, have an activity of the polypeptide). In one embodiment, the invention includes variants described

herein which hybridize under high stringency hybridization conditions (*e.g.*, for selective hybridization) to a nucleic acid sequence comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1 or 3 or the complement thereof. In another embodiment, the invention includes variants
5 described herein which hybridize under high stringency hybridization conditions (*e.g.*, for selective hybridization) to a nucleic acid sequence encoding an amino acid sequence of SEQ ID NO: 2 or a polymorphic variant thereof. In a preferred embodiment, the variant that hybridizes under high stringency hybridizations has an activity of a FLAP.

10 Such nucleic acid molecules can be detected and/or isolated by specific hybridization (*e.g.*, under high stringency conditions). “Specific hybridization,” as used herein, refers to the ability of a first nucleic acid to hybridize to a second nucleic acid in a manner such that the first nucleic acid does not hybridize to any nucleic acid other than to the second nucleic acid (*e.g.*, when
15 the first nucleic acid has a higher similarity to the second nucleic acid than to any other nucleic acid in a sample wherein the hybridization is to be performed). “Stringency conditions” for hybridization is a term of art which refers to the incubation and wash conditions, *e.g.*, conditions of temperature and buffer concentration, which permit hybridization of a particular nucleic acid to a
20 second nucleic acid; the first nucleic acid may be perfectly (*i.e.*, 100%) complementary to the second, or the first and second may share some degree of complementarity that is less than perfect (*e.g.*, 70%, 75%, 85%, 95%). For example, certain high stringency conditions can be used which distinguish perfectly complementary nucleic acids from those of less complementarity.
25 “High stringency conditions”, “moderate stringency conditions” and “low stringency conditions” for nucleic acid hybridizations are explained on pages 2.10.1-2.10.16 and pages 6.3.1-6.3.6 in *Current Protocols in Molecular Biology* (Ausubel, F.M. *et al.*, “*Current Protocols in Molecular Biology*”, John Wiley & Sons, (1998), the entire teachings of which are incorporated by reference
30 herein). The exact conditions which determine the stringency of hybridization depend not only on ionic strength (*e.g.*, 0.2X SSC, 0.1X SSC), temperature (*e.g.*, room temperature, 42°C, 68°C) and the concentration of destabilizing

agents such as formamide or denaturing agents such as SDS, but also on factors such as the length of the nucleic acid sequence, base composition, percent mismatch between hybridizing sequences and the frequency of occurrence of subsets of that sequence within other non-identical sequences. Thus, equivalent
5 conditions can be determined by varying one or more of these parameters while maintaining a similar degree of identity or similarity between the two nucleic acid molecules. Typically, conditions are used such that sequences at least about 60%, at least about 70%, at least about 80%, at least about 90% or at least about 95% or more identical to each other remain hybridized to one another.
10 By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, conditions which will allow a given sequence to hybridize (*e.g.*, selectively) with the most similar sequences in the sample can be determined.

Exemplary conditions are described in Krause, M.H. and S.A. Aaronson,
15 *Methods in Enzymology* 200: 546-556 (1991), and in, Ausubel, *et al.*, “*Current Protocols in Molecular Biology*”, John Wiley & Sons, (1998), which describes the determination of washing conditions for moderate or low stringency conditions. Washing is the step in which conditions are usually set so as to determine a minimum level of complementarity of the hybrids. Generally,
20 starting from the lowest temperature at which only homologous hybridization occurs, each °C by which the final wash temperature is reduced (holding SSC concentration constant) allows an increase by 1% in the maximum extent of mismatching among the sequences that hybridize. Generally, doubling the concentration of SSC results in an increase in T_m of -17°C. Using these
25 guidelines, the washing temperature can be determined empirically for high, moderate or low stringency, depending on the level of mismatch sought.

For example, a low stringency wash can comprise washing in a solution containing 0.2X SSC/0.1% SDS for 10 minutes at room temperature; a moderate stringency wash can comprise washing in a prewarmed solution
30 (42°C) solution containing 0.2X SSC/0.1% SDS for 15 minutes at 42°C; and a high stringency wash can comprise washing in prewarmed (68°C) solution containing 0.1X SSC/0.1%SDS for 15 minutes at 68°C. Furthermore, washes

can be performed repeatedly or sequentially to obtain a desired result as known in the art. Equivalent conditions can be determined by varying one or more of the parameters given as an example, as known in the art, while maintaining a similar degree of identity or similarity between the target nucleic acid molecule and the primer or probe used.

The percent homology or identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first sequence for optimal alignment). The nucleotides or amino acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions x 100). When a position in one sequence is occupied by the same nucleotide or amino acid residue as the corresponding position in the other sequence, then the molecules are homologous at that position. As used herein, nucleic acid or amino acid “homology” is equivalent to nucleic acid or amino acid “identity”. In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, for example, at least 40%, in certain embodiments at least 60%, and in other embodiments at least 70%, 80%, 90% or 95% of the length of the reference sequence. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A preferred, non-limiting example of such a mathematical algorithm is described in Karlin *et al.*, *Proc. Natl. Acad. Sci. USA* 90:5873-5877 (1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) as described in Altschul *et al.*, *Nucleic Acids Res.* 25:389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, NBLAST) can be used. In one embodiment, parameters for sequence comparison can be set at score=100, wordlength=12, or can be varied (*e.g.*, W=5 or W=20).

Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, *CABIOS* 4(1): 11-17 (1988). Such an algorithm is incorporated into the ALIGN

program (version 2.0) which is part of the GCG sequence alignment software package (Accelrys, Cambridge, UK). When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for
5 sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti, *Comput. Appl. Biosci.* 10:3-5 (1994); and FASTA described in Pearson and Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444-8 (1988).

In another embodiment, the percent identity between two amino acid
10 sequences can be accomplished using the GAP program in the GCG software package using either a BLOSUM63 matrix or a PAM250 matrix, and a gap weight of 12, 10, 8, 6, or 4 and a length weight of 2, 3, or 4. In yet another embodiment, the percent identity between two nucleic acid sequences can be accomplished using the GAP program in the GCG software package using a gap
15 weight of 50 and a length weight of 3.

The present invention also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleic acid sequence comprising SEQ ID NO: 1 or 3 or the complement of
20 SEQ ID NO: 1 or 3, and also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleic acid sequence encoding an amino acid sequence of the invention or polymorphic variant thereof. The nucleic acid fragments of the invention are at least about 15, for example, at least about 18, 20, 23 or 25 nucleotides, and can be 30, 40, 50, 100, 200 or more nucleotides in length. Longer fragments, for
25 example, 30 or more nucleotides in length, encoding antigenic polypeptides described herein are particularly useful, such as for the generation of antibodies as described below.

Probes and Primers

30 In a related aspect, the nucleic acid fragments of the invention are used as probes or primers in assays such as those described herein. "Probes" or "primers" are oligonucleotides that hybridize in a base-specific manner to a

complementary strand of nucleic acid molecules. Such probes and primers include polypeptide nucleic acids, as described in Nielsen *et al.*, (*Science* 254:1497-1500 (1991)).

5 A probe or primer comprises a region of nucleic acid that hybridizes to at least about 15, for example about 20-25, and in certain embodiments about 40, 50 or 75, consecutive nucleotides of a nucleic acid of the invention, such as a nucleic acid comprising a contiguous nucleic acid sequence of SEQ ID NOs: 1 or 3 or the complement of SEQ ID Nos: 1 or 3, or a nucleic acid sequence encoding an amino acid sequence of SEQ ID NO: 2 or polymorphic variant
10 thereof. In preferred embodiments, a probe or primer comprises 100 or fewer nucleotides, in certain embodiments, from 6 to 50 nucleotides, for example, from 12 to 30 nucleotides. In other embodiments, the probe or primer is at least 70% identical to the contiguous nucleic acid sequence or to the complement of the contiguous nucleotide sequence, for example, at least 80% identical, in
15 certain embodiments at least 90% identical, and in other embodiments at least 95% identical, or even capable of selectively hybridizing to the contiguous nucleic acid sequence or to the complement of the contiguous nucleotide sequence. Often, the probe or primer further comprises a label, *e.g.*, radioisotope, fluorescent compound, enzyme, or enzyme co-factor.

20 The nucleic acid molecules of the invention such as those described above can be identified and isolated using standard molecular biology techniques and the sequence information provided herein. For example, nucleic acid molecules can be amplified and isolated using the polymerase chain reaction and synthetic oligonucleotide primers based on one or more of SEQ ID
25 NOs: 1 or 3, or the complement thereof, or designed based on nucleotides based on sequences encoding one or more of the amino acid sequences provided herein. See generally *PCR Technology: Principles and Applications for DNA Amplification* (ed. H.A. Erlich, Freeman Press, NY, NY, 1992); *PCR Protocols: A Guide to Methods and Applications* (Eds. Innis *et al.*, Academic Press, San
30 Diego, CA, 1990); Mattila *et al.*, *Nucl. Acids Res.* 19:4967 (1991); Eckert *et al.*, *PCR Methods and Applications* 1:17 (1991); PCR (eds. McPherson *et al.*, IRL Press, Oxford); and U.S. Patent 4,683,202. The nucleic acid molecules can be

amplified using cDNA, mRNA or genomic DNA as a template, cloned into an appropriate vector and characterized by DNA sequence analysis.

Other suitable amplification methods include the ligase chain reaction (LCR) (see Wu and Wallace, *Genomics* 4:560 (1989), Landegren *et al.*, *Science* 241:1077 (1988), transcription amplification (Kwoh *et al.*, *Proc. Natl. Acad. Sci. USA* 86:1173 (1989)), and self-sustained sequence replication (Guatelli *et al.*, *Proc. Nat. Acad. Sci. USA* 87:1874 (1990)) and nucleic acid based sequence amplification (NASBA). The latter two amplification methods involve isothermal reactions based on isothermal transcription, which produce both single stranded RNA (ssRNA) and double stranded DNA (dsDNA) as the amplification products in a ratio of about 30 or 100 to 1, respectively.

The amplified DNA can be labeled, for example, radiolabeled, and used as a probe for screening a cDNA library derived from human cells, mRNA in zap express, ZIPLOX or other suitable vector. Corresponding clones can be isolated, DNA can be obtained following *in vivo* excision, and the cloned insert can be sequenced in either or both orientations by art recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. For example, the direct analysis of the nucleic acid molecules of the present invention can be accomplished using well-known methods that are commercially available. See, for example, Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (2nd Ed., CSHP, New York 1989); Zyskind *et al.*, *Recombinant DNA Laboratory Manual*, (Acad. Press, 1988)). Using these or similar methods, the polypeptide and the DNA encoding the polypeptide can be isolated, sequenced and further characterized.

Antisense nucleic acid molecules of the invention can be designed using the nucleotide sequences of SEQ ID NOs: 1 or 3 and/or the complement of one or more of SEQ ID NOs: 1 or 3 and/or a portion of one or more of SEQ ID NOs: 1 or 3 or the complement of one or more of SEQ ID NOs: 1 or 3 and/or a sequence encoding the amino acid sequences of SEQ ID NOs: 2 or encoding a portion of one or more of SEQ ID NOs: 1 or 3 or their complement. They can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid molecule

(*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the antisense nucleic acid molecule can be produced biologically using an expression vector into which a nucleic acid molecule has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid molecule will be of an antisense orientation to a target nucleic acid of interest).

The nucleic acid sequences can also be used to compare with endogenous DNA sequences in patients to identify one or more of the disorders related to FLAP, and as probes, such as to hybridize and discover related DNA sequences or to subtract out known sequences from a sample. The nucleic acid sequences can further be used to derive primers for genetic fingerprinting, to raise anti-polypeptide antibodies using DNA immunization techniques, and as an antigen to raise anti-DNA antibodies or elicit immune responses. Portions or fragments of the nucleotide sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions or nucleic acid regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. Additionally, the nucleotide sequences of the invention can be used to identify and express recombinant polypeptides for analysis, characterization or therapeutic use, or as markers for tissues in which the corresponding polypeptide is expressed, either constitutively, during tissue differentiation, or in diseased states. The nucleic acid sequences can additionally be used as reagents in the screening and/or diagnostic assays described herein, and can also be included as components of kits (*e.g.*, reagent kits) for use in the screening and/or diagnostic assays described herein.

Vectors

Another aspect of the invention pertains to nucleic acid constructs containing a nucleic acid molecule of SEQ ID NOs: 1 or 3 or the complement thereof (or a portion thereof). Yet another aspect of the invention pertains to
5 nucleic acid constructs containing a nucleic acid molecule encoding an amino acid of SEQ ID NO: 2 or polymorphic variant thereof. The constructs comprise a vector (*e.g.*, an expression vector) into which a sequence of the invention has been inserted in a sense or antisense orientation. As used herein, the term “vector” refers to a nucleic acid molecule capable of transporting another
10 nucleic acid to which it has been linked. One type of vector is a “plasmid”, which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are
15 introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, such as expression vectors, are capable of directing the
20 expression of genes or nucleic acids to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses) that serve
25 equivalent functions.

Preferred recombinant expression vectors of the invention comprise a nucleic acid molecule of the invention in a form suitable for expression of the nucleic acid molecule in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the
30 basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, “operably linked” or “operatively linked” is intended to mean that the nucleic

acid sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleic acid sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term “regulatory sequence” is intended to include
5 promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, “Gene Expression Technology”, *Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleic acid sequence in many
10 types of host cell and those which direct expression of the nucleic acid sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed and the level of expression of polypeptide desired. The expression vectors of the
15 invention can be introduced into host cells to thereby produce polypeptides, including fusion polypeptides, encoded by nucleic acid molecules as described herein.

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic or eukaryotic cells,
20 *e.g.*, bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

25 Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms “host cell” and “recombinant host cell” are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications
30 may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

5 A host cell can be any prokaryotic or eukaryotic cell. For example, a nucleic acid molecule of the invention can be expressed in bacterial cells (*e.g.*, *E. coli*), insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

10 Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms “transformation” and “transfection” are intended to refer to a variety of art-recognized techniques for introducing a foreign nucleic acid molecule (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

15 For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene or nucleic acid that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene or nucleic acid of interest. Preferred
20 selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid molecules encoding a selectable marker can be introduced into a host cell on the same vector as the nucleic acid molecule of the invention or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid molecule can be identified by
25 drug selection (*e.g.*, cells that have incorporated the selectable marker gene or nucleic acid will survive, while the other cells die).

30 A host cell of the invention, such as a prokaryotic host cell or eukaryotic host cell in culture can be used to produce (*i.e.*, express) a polypeptide of the invention. Accordingly, the invention further provides methods for producing a polypeptide using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a polypeptide of the invention has been introduced)

in a suitable medium such that the polypeptide is produced. In another embodiment, the method further comprises isolating the polypeptide from the medium or the host cell.

5 The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a nucleic acid molecule of the invention has been introduced (*e.g.*, an exogenous FLAP nucleic acid, or an exogenous nucleic acid encoding a FLAP polypeptide). Such host cells can then be used to create non-human transgenic animals in which exogenous nucleotide sequences have been introduced into the genome or homologous recombinant animals in which endogenous nucleotide sequences have been altered. Such animals are useful for studying the function and/or activity of the nucleic acid sequence and polypeptide encoded by the sequence and for identifying and/or evaluating modulators of their activity. As used 10 herein, a “transgenic animal” is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal include a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens and amphibians. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a “homologous recombinant animal” is a non-human animal, preferably a mammal, more preferably a mouse, in which an 25 endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

30 Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Pat. No. 4,873,191 and in Hogan, *Manipulating the Mouse*

Embryo (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, *Current Opinion in BioTechnology* 2:823-829 (1991) and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169. Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.*, *Nature* 385:810-813 (1997) and PCT Publication Nos. WO 97/07668 and WO 97/07669.

POLYPEPTIDES OF THE INVENTION

The present invention also pertains to isolated polypeptides encoded by FLAP nucleic acids ("FLAP polypeptides"), and fragments and variants thereof, as well as polypeptides encoded by nucleotide sequences described herein (*e.g.*, other splicing variants). The term "polypeptide" refers to a polymer of amino acids, and not to a specific length; thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. As used herein, a polypeptide is said to be "isolated" or "purified" when it is substantially free of cellular material when it is isolated from recombinant and non-recombinant cells, or free of chemical precursors or other chemicals when it is chemically synthesized. A polypeptide, however, can be joined to another polypeptide with which it is not normally associated in a cell (*e.g.*, in a "fusion protein") and still be "isolated" or "purified."

The polypeptides of the invention can be purified to homogeneity. It is understood, however, that preparations in which the polypeptide is not purified to homogeneity are useful. The critical feature is that the preparation allows for the desired function of the polypeptide, even in the presence of considerable amounts of other components. Thus, the invention encompasses various degrees of purity. In one embodiment, the language "substantially free of cellular material" includes preparations of the polypeptide having less than about 30% (by dry weight) other proteins (*i.e.*, contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins.

When a polypeptide is recombinantly produced, it can also be substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, less than about 10%, or less than about 5% of the volume of the polypeptide preparation. The language “substantially free of chemical precursors or other chemicals” includes preparations of the polypeptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language “substantially free of chemical precursors or other chemicals” includes preparations of the polypeptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

In one embodiment, a polypeptide of the invention comprises an amino acid sequence encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1 or 3, or the complement of SEQ ID NO: 1 or 3, or portions thereof, or a portion or polymorphic variant thereof. However, the polypeptides of the invention also encompass fragment and sequence variants. Variants include a substantially homologous polypeptide encoded by the same genetic locus in an organism, *i.e.*, an allelic variant, as well as other splicing variants. Variants also encompass polypeptides derived from other genetic loci in an organism, but having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1 or 3 or their complement, or portions thereof, or having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of nucleotide sequences encoding SEQ ID NO: 2 or polymorphic variants thereof. Variants also include polypeptides substantially homologous or identical to these polypeptides but derived from another organism, *i.e.*, an ortholog. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by chemical synthesis. Variants also include

polypeptides that are substantially homologous or identical to these polypeptides that are produced by recombinant methods.

As used herein, two polypeptides (or a region of the polypeptides) are substantially homologous or identical when the amino acid sequences are at least about 45-55%, in certain embodiments at least about 70-75%, and in other
5 embodiments at least about 80-85%, and in others greater than about 90% or more homologous or identical. A substantially homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid molecule hybridizing to SEQ ID NO: 1 or 3 or portion thereof, under stringent
10 conditions as more particularly described above, or will be encoded by a nucleic acid molecule hybridizing to a nucleic acid sequence encoding SEQ ID NO: 2 or a portion thereof or polymorphic variant thereof, under stringent conditions as more particularly described thereof.

The invention also encompasses polypeptides having a lower degree of identity but having sufficient similarity so as to perform one or more of the
15 same functions performed by a polypeptide encoded by a nucleic acid molecule of the invention. Similarity is determined by conserved amino acid substitution. Such substitutions are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Conservative substitutions are
20 likely to be phenotypically silent. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the
25 aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, *Science* 247:1306-1310 (1990).

A variant polypeptide can differ in amino acid sequence by one or more substitutions, deletions, insertions, inversions, fusions, and truncations or a
30 combination of any of these. Further, variant polypeptides can be fully functional or can lack function in one or more activities. Fully functional variants typically contain only conservative variation or variation in non-critical

residues or in non-critical regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree. Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncation or a substitution, insertion, inversion, or deletion in a critical residue or critical region.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity *in vitro*, or *in vitro* proliferative activity. Sites that are critical for polypeptide activity can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al.*, *J. Mol. Biol.* 224:899-904 (1992); de Vos *et al.*, *Science* 255:306-312 (1992)).

The invention also includes fragments of the polypeptides of the invention. Fragments can be derived from a polypeptide encoded by a nucleic acid molecule comprising SEQ ID NO: 1 or 3, or the complement of SEQ ID NO: 1 or 3 (or other variants). However, the invention also encompasses fragments of the variants of the polypeptides described herein. As used herein, a fragment comprises at least 6 contiguous amino acids. Useful fragments include those that retain one or more of the biological activities of the polypeptide as well as fragments that can be used as an immunogen to generate polypeptide-specific antibodies.

Biologically active fragments (peptides which are, for example, 6, 9, 12, 15, 16, 20, 30, 35, 36, 37, 38, 39, 40, 50, 100 or more amino acids in length) can comprise a domain, segment, or motif that has been identified by analysis of the polypeptide sequence using well-known methods, *e.g.*, signal peptides, extracellular domains, one or more transmembrane segments or loops, ligand binding regions, zinc finger domains, DNA binding domains, acylation sites, glycosylation sites, or phosphorylation sites.

Fragments can be discrete (not fused to other amino acids or polypeptides) or can be within a larger polypeptide. Further, several fragments can be comprised within a single larger polypeptide. In one embodiment a fragment designed for expression in a host can have heterologous pre- and pro-
5 polypeptide regions fused to the amino terminus of the polypeptide fragment and an additional region fused to the carboxyl terminus of the fragment.

The invention thus provides chimeric or fusion polypeptides. These comprise a polypeptide of the invention operatively linked to a heterologous protein or polypeptide having an amino acid sequence not substantially
10 homologous to the polypeptide. "Operatively linked" indicates that the polypeptide and the heterologous protein are fused in-frame. The heterologous protein can be fused to the N-terminus or C-terminus of the polypeptide. In one embodiment the fusion polypeptide does not affect function of the polypeptide *per se*. For example, the fusion polypeptide can be a GST-fusion polypeptide in
15 which the polypeptide sequences are fused to the C-terminus of the GST sequences. Other types of fusion polypeptides include, but are not limited to, enzymatic fusion polypeptides, for example beta-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions and Ig fusions. Such fusion polypeptides, particularly poly-His fusions, can facilitate the purification of
20 recombinant polypeptide. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of a polypeptide can be increased using a heterologous signal sequence. Therefore, in another embodiment, the fusion polypeptide contains a heterologous signal sequence at its N-terminus.

EP-A-O 464 533 discloses fusion proteins comprising various portions
25 of immunoglobulin constant regions. The Fc is useful in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262). In drug discovery, for example, human proteins have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists. Bennett *et al.*, *Journal of Molecular Recognition*, 8:52-58 (1995)
30 and Johanson *et al.*, *The Journal of Biological Chemistry*, 270, 16:9459-9471 (1995). Thus, this invention also encompasses soluble fusion polypeptides containing a polypeptide of the invention and various portions of the constant

regions of heavy or light chains of immunoglobulins of various subclasses (IgG, IgM, IgA, IgE).

A chimeric or fusion polypeptide can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the
5 different polypeptide sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of nucleic acid fragments can be carried out using anchor primers which give rise to complementary overhangs between two
10 consecutive nucleic acid fragments which can subsequently be annealed and re-amplified to generate a chimeric nucleic acid sequence (see Ausubel *et al.*, *Current Protocols in Molecular Biology*, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST protein). A nucleic acid molecule encoding a polypeptide of the invention
15 can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide.

The isolated polypeptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. In one embodiment, the
20 polypeptide is produced by recombinant DNA techniques. For example, a nucleic acid molecule encoding the polypeptide is cloned into an expression vector, the expression vector introduced into a host cell and the polypeptide expressed in the host cell. The polypeptide can then be isolated from the cells by an appropriate purification scheme using standard protein purification
25 techniques.

The polypeptides of the present invention can be used to raise antibodies or to elicit an immune response. The polypeptides can also be used as a reagent, *e.g.*, a labeled reagent, in assays to quantitatively determine levels of the polypeptide or a molecule to which it binds (*e.g.*, a ligand) in biological
30 fluids. The polypeptides can also be used as markers for cells or tissues in which the corresponding polypeptide is preferentially expressed, either constitutively, during tissue differentiation, or in diseased states. The

polypeptides can be used to isolate a corresponding binding agent, *e.g.*, ligand, such as, for example, in an interaction trap assay, and to screen for peptide or small molecule antagonists or agonists of the binding interaction. For example, because members of the leukotriene pathway including FLAP bind to receptors, the leukotriene pathway polypeptides can be used to isolate such receptors.

ANTIBODIES OF THE INVENTION

Polyclonal and/or monoclonal antibodies that specifically bind one form of the polypeptide or nucleic acid product (*e.g.*, a polypeptide encoded by a nucleic acid having a SNP as set forth in Table 13), but not to another form of the polypeptide or nucleic acid product, are also provided. Antibodies are also provided which bind a portion of either polypeptide encoded by nucleic acids of the invention (*e.g.*, SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3), or to a polypeptide encoded by nucleic acids of the invention that contain a polymorphic site or sites. The invention also provides antibodies to the polypeptides and polypeptide fragments of the invention, or a portion thereof, or having an amino acid sequence encoded by a nucleic acid molecule comprising all or a portion of SEQ ID NOs: 1 or 3, or the complement thereof, or another variant or portion thereof.

The term “antibody” as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that specifically binds an antigen. A molecule that specifically binds to a polypeptide of the invention is a molecule that binds to that polypeptide or a fragment thereof, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the polypeptide. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')₂ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind to a polypeptide of the invention. The term “monoclonal antibody” or “monoclonal antibody composition”, as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of

immunoreacting with a particular epitope of a polypeptide of the invention. A monoclonal antibody composition thus typically displays a single binding affinity for a particular polypeptide of the invention with which it immunoreacts.

5 Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a desired immunogen, *e.g.*, polypeptide of the invention or fragment thereof. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If
10 desired, the antibody molecules directed against the polypeptide can be isolated from the mammal (*e.g.*, from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, *e.g.*, when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare
15 monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, *Nature* 256:495-497 (1975), the human B cell hybridoma technique (Kozbor *et al.*, *Immunol. Today* 4:72 (1983)); the EBV-hybridoma technique (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, 1985, Inc., pp. 77-96); or trioma techniques.
20 The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology* (1994) Coligan *et al.* (eds.) John Wiley & Sons, Inc., New York, NY). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as described above, and the culture supernatants of the resulting
25 hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds a polypeptide of the invention.

 Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody to a polypeptide of the invention (see, *e.g.*, *Current*
30 *Protocols in Immunology*, *supra*; Galfre *et al.*, *Nature* 266:55052 (1977); R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); and Lerner, *Yale J.*

Biol. Med. 54:387-402 (1981). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods that also would be useful.

5 Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the polypeptide to thereby isolate immunoglobulin library members that bind the polypeptide. Kits for generating and screening phage display libraries are commercially available (e.g., the
10 Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™* Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT
15 Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.*, *Bio/Technology* 9: 1370-1372 (1991); Hay *et al.*, *Hum. Antibod. Hybridomas* 3:81-85 (1992); Huse *et al.*,
20 *Science* 246:1275-1281 (1989); Griffiths *et al.*, *EMBO J.* 12:725-734 (1993).

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be
25 produced by recombinant DNA techniques known in the art.

In general, antibodies of the invention (e.g., a monoclonal antibody) can be used to isolate a polypeptide of the invention by standard techniques, such as affinity chromatography or immunoprecipitation. A polypeptide-specific antibody can facilitate the purification of natural polypeptide from cells and of
30 recombinantly produced polypeptide expressed in host cells. Moreover, an antibody specific for a polypeptide of the invention can be used to detect the polypeptide (e.g., in a cellular lysate, cell supernatant, or tissue sample) in order

to evaluate the abundance and pattern of expression of the polypeptide.

Antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

As described above, antibodies to leukotrienes can be used in the methods of the invention. The methods described herein can be used to generate such antibodies for use in the methods.

DIAGNOSTIC ASSAYS

The nucleic acids, probes, primers, polypeptides and antibodies described herein can be used in methods of diagnosis of a susceptibility to MI, ACS, stroke or PAOD, or to another disease or condition associated with an MI gene, such as FLAP, as well as in kits useful for diagnosis of a susceptibility to MI, ACS, stroke or PAOD, or to another disease or condition associated with FLAP. In one embodiment, the kit useful for diagnosis of susceptibility to MI, ACS, stroke or PAOD, or to another disease or condition associated with FLAP comprises primers as described herein, wherein the primers contain one or more of the SNPs identified in Table 13.

In one embodiment of the invention, diagnosis of susceptibility to MI, ACS, stroke or PAOD (or diagnosis of susceptibility to another disease or condition associated with FLAP), is made by detecting a polymorphism in a

FLAP nucleic acid as described herein. The polymorphism can be an alteration in a FLAP nucleic acid, such as the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift alteration; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of the gene or nucleic acid; duplication of all or a part of the gene or nucleic acid; transposition of all or a part of the gene or nucleic acid; or rearrangement of all or a part of the gene or nucleic acid. More than one such alteration may be present in a single gene or nucleic acid. Such sequence changes cause an alteration in the polypeptide encoded by a FLAP nucleic acid. For example, if the alteration is a frame shift alteration, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with a disease or condition associated with a FLAP nucleic acid or a susceptibility to a disease or condition associated with a FLAP nucleic acid can be a synonymous alteration in one or more nucleotides (*i.e.*, an alteration that does not result in a change in the polypeptide encoded by a FLAP nucleic acid). Such a polymorphism may alter splicing sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the nucleic acid. A FLAP nucleic acid that has any of the alteration described above is referred to herein as an "altered nucleic acid."

In a first method of diagnosing a susceptibility to MI, ACS, stroke or PAOD, hybridization methods, such as Southern analysis, Northern analysis, or *in situ* hybridizations, can be used (see *Current Protocols in Molecular Biology*, Ausubel, F. *et al.*, eds., John Wiley & Sons, including all supplements through 1999). For example, a biological sample from a test subject (a "test sample") of genomic DNA, RNA, or cDNA, is obtained from an individual suspected of having, being susceptible to or predisposed for, or carrying a defect for, a

susceptibility to a disease or condition associated with a FLAP nucleic acid (the “test individual”). The individual can be an adult, child, or fetus. The test sample can be from any source which contains genomic DNA, such as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from skin, muscle, buccal or conjunctival mucosa, placenta, gastrointestinal tract or other organs. A test sample of DNA from fetal cells or tissue can be obtained by appropriate methods, such as by amniocentesis or chorionic villus sampling. The DNA, RNA, or cDNA sample is then examined to determine whether a polymorphism in an MI nucleic acid is present, and/or to determine which splicing variant(s) encoded by the FLAP is present. The presence of the polymorphism or splicing variant(s) can be indicated by hybridization of the nucleic acid in the genomic DNA, RNA, or cDNA to a nucleic acid probe. A “nucleic acid probe,” as used herein, can be a DNA probe or an RNA probe; the nucleic acid probe can contain at least one polymorphism in a FLAP nucleic acid or contains a nucleic acid encoding a particular splicing variant of a FLAP nucleic acid. The probe can be any of the nucleic acid molecules described above (e.g., the nucleic acid, a fragment, a vector comprising the nucleic acid, a probe or primer, etc.).

To diagnose a susceptibility to MI, ACS, stroke or PAOD (or another disease or condition associated with FLAP), the test sample containing a FLAP nucleic acid is contacted with at least one nucleic acid probe to form a hybridization sample. A preferred probe for detecting mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to mRNA or genomic DNA sequences described herein. The nucleic acid probe can be, for example, a full-length nucleic acid molecule, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to appropriate mRNA or genomic DNA. For example, the nucleic acid probe can be all or a portion of one of SEQ ID NOs: 1 and 3, or the complement thereof or a portion thereof; or can be a nucleic acid encoding all or a portion of one of SEQ ID NO: 2. Other suitable probes for use in the diagnostic assays of the invention are

described above (see *e.g.*, probes and primers discussed under the heading, “Nucleic Acids of the Invention”).

The hybridization sample is maintained under conditions that are sufficient to allow specific hybridization of the nucleic acid probe to a FLAP nucleic acid. “Specific hybridization,” as used herein, indicates exact
5 hybridization (*e.g.*, with no mismatches). Specific hybridization can be performed under high stringency conditions or moderate stringency conditions, for example, as described above. In a particularly preferred embodiment, the hybridization conditions for specific hybridization are high stringency.

Specific hybridization, if present, is then detected using standard
10 methods. If specific hybridization occurs between the nucleic acid probe and FLAP nucleic acid in the test sample, then the FLAP has the polymorphism, or is the splicing variant, that is present in the nucleic acid probe. More than one nucleic acid probe can also be used concurrently in this method. Specific
15 hybridization of any one of the nucleic acid probes is indicative of a polymorphism in the FLAP nucleic acid, or of the presence of a particular splicing variant encoding the FLAP nucleic acid, and is therefore diagnostic for a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD).

In Northern analysis (see *Current Protocols in Molecular Biology*, Ausubel, F. *et al.*, eds., John Wiley & Sons, *supra*) the hybridization methods described above are used to identify the presence of a polymorphism or a particular splicing variant, associated with a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD). For
20 Northern analysis, a test sample of RNA is obtained from the individual by appropriate means. Specific hybridization of a nucleic acid probe, as described above, to RNA from the individual is indicative of a polymorphism in a FLAP nucleic acid, or of the presence of a particular splicing variant encoded by a FLAP nucleic acid, and is therefore diagnostic for susceptibility to a disease or
25 condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD).
30

For representative examples of use of nucleic acid probes, see, for example, U.S. Patents No. 5,288,611 and 4,851,330.

Alternatively, a peptide nucleic acid (PNA) probe can be used instead of a nucleic acid probe in the hybridization methods described above. PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen, P.E. *et al.*, *Bioconjugate Chemistry* 5, American Chemical Society, p. 1 (1994)). The PNA probe can be designed to specifically hybridize to a nucleic acid having a polymorphism associated with a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI). Hybridization of the PNA probe to a FLAP nucleic acid as described herein is diagnostic for the susceptibility to the disease or condition.

In another method of the invention, mutation analysis by restriction digestion can be used to detect an altered nucleic acid, or nucleic acids containing a polymorphism(s), if the mutation or polymorphism in the nucleic acid results in the creation or elimination of a restriction site. A test sample containing genomic DNA is obtained from the individual. Polymerase chain reaction (PCR) can be used to amplify a FLAP nucleic acid (and, if necessary, the flanking sequences) in the test sample of genomic DNA from the test individual. RFLP analysis is conducted as described (see *Current Protocols in Molecular Biology, supra*). The digestion pattern of the relevant DNA fragment indicates the presence or absence of the alteration or polymorphism in the FLAP nucleic acid, and therefore indicates the presence or absence of the susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD).

Sequence analysis can also be used to detect specific polymorphisms in the FLAP nucleic acid. A test sample of DNA or RNA is obtained from the test individual. PCR or other appropriate methods can be used to amplify the nucleic acid, and/or its flanking sequences, if desired. The sequence of a FLAP nucleic acid, or a fragment of the nucleic acid, or cDNA, or fragment of the cDNA, or mRNA, or fragment of the mRNA, is determined, using standard methods. The sequence of the nucleic acid, nucleic acid fragment, cDNA, cDNA fragment, mRNA, or mRNA fragment is compared with the known

nucleic acid sequence of the nucleic acid, cDNA (*e.g.*, one or more of SEQ ID NOs: 1 or 3, and/or the complement of SEQ ID NO: 1 or 3), or a nucleic acid sequence encoding SEQ ID NO: 2 or a fragment thereof) or mRNA, as appropriate. The presence of a polymorphism in the FLAP indicates that the individual has a susceptibility to a disease associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD).

Allele-specific oligonucleotides can also be used to detect the presence of polymorphism(s) in the FLAP nucleic acid, through the use of dot-blot hybridization of amplified oligonucleotides with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki, R. *et al.*, *Nature* 324:163-166 (1986)). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs, for example, approximately 15-30 base pairs, that specifically hybridizes to a FLAP nucleic acid, and that contains a polymorphism associated with a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD). An allele-specific oligonucleotide probe that is specific for particular polymorphisms in a FLAP nucleic acid can be prepared, using standard methods (see *Current Protocols in Molecular Biology, supra*). To identify polymorphisms in the nucleic acid associated with susceptibility to disease, a test sample of DNA is obtained from the individual. PCR can be used to amplify all or a fragment of a FLAP nucleic acid, and its flanking sequences. The DNA containing the amplified FLAP nucleic acid (or fragment of the nucleic acid) is dot-blotted, using standard methods (see *Current Protocols in Molecular Biology, supra*), and the blot is contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified FLAP is then detected. Specific hybridization of an allele-specific oligonucleotide probe to DNA from the individual is indicative of a polymorphism in the FLAP, and is therefore indicative of a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD).

An allele-specific primer hybridizes to a site on target DNA overlapping a polymorphism and only primes amplification of an allelic form to which the primer exhibits perfect complementarity. See Gibbs, *Nucleic Acid Res.* 17,

2427-2448 (1989). This primer is used in conjunction with a second primer which hybridizes at a distal site. Amplification proceeds from the two primers, resulting in a detectable product which indicates the particular allelic form is present. A control is usually performed with a second pair of primers, one of which shows a single base mismatch at the polymorphic site and the other of which exhibits perfect complementarity to a distal site. The single-base mismatch prevents amplification and no detectable product is formed. The method works best when the mismatch is included in the 3'-most position of the oligonucleotide aligned with the polymorphism because this position is most destabilizing to elongation from the primer (see, *e.g.*, WO 93/22456).

With the addition of such analogs as locked nucleic acids (LNAs), the size of primers and probes can be reduced to as few as 8 bases. LNAs are a novel class of bicyclic DNA analogs in which the 2' and 4' positions in the furanose ring are joined via an O-methylene (oxy-LNA), S-methylene (thio-LNA), or amino methylene (amino-LNA) moiety. Common to all of these LNA variants is an affinity toward complementary nucleic acids, which is by far the highest reported for a DNA analog. For example, particular all oxy-LNA nonamers have been shown to have melting temperatures of 64°C and 74°C when in complex with complementary DNA or RNA, respectively, as opposed to 28°C for both DNA and RNA for the corresponding DNA nonamer. Substantial increases in T_m are also obtained when LNA monomers are used in combination with standard DNA or RNA monomers. For primers and probes, depending on where the LNA monomers are included (*e.g.*, the 3' end, the 5' end, or in the middle), the T_m could be increased considerably.

In another embodiment, arrays of oligonucleotide probes that are complementary to target nucleic acid sequence segments from an individual, can be used to identify polymorphisms in a FLAP nucleic acid. For example, in one embodiment, an oligonucleotide array can be used. Oligonucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. These oligonucleotide arrays, also described as "Genechips™," have been generally described in the art, for example, U.S. Pat. No. 5,143,854 and PCT patent

publication Nos. WO 90/15070 and WO 92/10092. These arrays can generally be produced using mechanical synthesis methods or light directed synthesis methods that incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis methods. See Fodor *et al.*, *Science* 251:767-777 (1991); Pirrung *et al.*, U.S. Pat. 5,143,854; (see also PCT Application WO 90/15070); Fodor *et al.*, PCT Publication WO 92/10092; and U.S. Pat. 5,424,186, the entire teachings of each of which are incorporated by reference herein. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, *e.g.*, U.S. Pat. 5,384,261, the entire teachings of which are incorporated by reference herein. In another example, linear arrays can be utilized.

Once an oligonucleotide array is prepared, a nucleic acid of interest is hybridized with the array and scanned for polymorphisms. Hybridization and scanning are generally carried out by methods described herein and also in, *e.g.*, published PCT Application Nos. WO 92/10092 and WO 95/11995, and U.S. Pat. No. 5,424,186, the entire teachings of which are incorporated by reference herein. In brief, a target nucleic acid sequence that includes one or more previously identified polymorphic markers is amplified using well-known amplification techniques, *e.g.*, PCR. Typically, this involves the use of primer sequences that are complementary to the two strands of the target sequence both upstream and downstream from the polymorphism. Asymmetric PCR techniques may also be used. Amplified target, generally incorporating a label, is then hybridized with the array under appropriate conditions. Upon completion of hybridization and washing of the array, the array is scanned to determine the position on the array to which the target sequence hybridizes. The hybridization data obtained from the scan is typically in the form of fluorescence intensities as a function of location on the array. In a reverse method, a probe, containing a polymorphism, can be coupled to a solid surface and PCR amplicons are then added to hybridize to these probes.

Although primarily described in terms of a single detection block, *e.g.*, detection of a single polymorphism arrays can include multiple detection blocks, and thus be capable of analyzing multiple, specific polymorphisms. It

will generally be understood that detection blocks may be grouped within a single array or in multiple, separate arrays so that varying, optimal conditions may be used during the hybridization of the target to the array. For example, it may often be desirable to provide for the detection of those polymorphisms that
5 fall within G-C rich stretches of a genomic sequence, separately from those falling in A-T rich segments. This allows for the separate optimization of hybridization conditions for each situation.

Additional uses of oligonucleotide arrays for detection of polymorphisms can be found, for example, in U.S. Patents Nos. 5,858,659 and
10 5,837,832, the entire teachings of which are incorporated by reference herein. Other methods of nucleic acid analysis can be used to detect polymorphisms in a nucleic acid described herein, or variants encoded by a nucleic acid described herein. Representative methods include direct manual sequencing (Church and Gilbert, *Proc. Natl. Acad. Sci. USA* 81:1991-1995 (1988); Sanger, F. *et al.*,
15 *Proc. Natl. Acad. Sci., USA* 74:5463-5467 (1977); Beavis *et al.* U.S. Pat. No. 5,288,644); automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCP); clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE) (Sheffield, V.C. *et al.*, *Proc. Natl. Acad. Sci. USA* 86:232-236 (1989)), mobility shift analysis (Orita, M. *et al.*, *Proc. Natl. Acad. Sci. USA* 86:2766-2770 (1989)), restriction enzyme
20 analysis (Flavell *et al.*, *Cell* 15:25 (1978); Geever, *et al.*, *Proc. Natl. Acad. Sci. USA* 78:5081 (1981)); heteroduplex analysis; chemical mismatch cleavage (CMC) (Cotton *et al.*, *Proc. Natl. Acad. Sci. USA* 85:4397-4401 (1985)); RNase protection assays (Myers, R.M. *et al.*, *Science* 230:1242 (1985)); use of
25 polypeptides which recognize nucleotide mismatches, such as *E. coli* mutS protein; allele-specific PCR, for example.

In one embodiment of the invention, diagnosis of a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD) can also be made by expression analysis by quantitative PCR (kinetic thermal
30 cycling). This technique utilizing TaqMan[®] can be used to allow the identification of polymorphisms and whether a patient is homozygous or heterozygous. The technique can assess the presence of an alteration in the

expression or composition of the polypeptide encoded by a FLAP nucleic acid or splicing variants encoded by a FLAP nucleic acid. Further, the expression of the variants can be quantified as physically or functionally different.

5 In another embodiment of the invention, diagnosis of a susceptibility to MI, ACS, stroke or PAOD (or of another disease or condition associated with FLAP) can also be made by examining expression and/or composition of a FLAP polypeptide, by a variety of methods, including enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. A test sample from an individual is assessed for the
10 presence of an alteration in the expression and/or an alteration in composition of the polypeptide encoded by a FLAP nucleic acid, or for the presence of a particular variant encoded by a FLAP nucleic acid. An alteration in expression of a polypeptide encoded by a FLAP nucleic acid can be, for example, an alteration in the quantitative polypeptide expression (*i.e.*, the amount of
15 polypeptide produced); an alteration in the composition of a polypeptide encoded by a FLAP nucleic acid is an alteration in the qualitative polypeptide expression (*e.g.*, expression of an altered FLAP polypeptide or of a different splicing variant). In a preferred embodiment, diagnosis of a susceptibility to a disease or condition associated with FLAP is made by detecting a particular
20 splicing variant encoded by that FLAP variant, or a particular pattern of splicing variants.

Both such alterations (quantitative and qualitative) can also be present. An “alteration” in the polypeptide expression or composition, refers to an alteration in expression or composition in a test sample, as compared with the
25 expression or composition of polypeptide by a FLAP nucleic acid in a control sample. A control sample is a sample that corresponds to the test sample (*e.g.*, is from the same type of cells), and is from an individual who is not affected by the disease or a susceptibility to a disease or condition associated with a FLAP nucleic acid. An alteration in the expression or composition of the polypeptide
30 in the test sample, as compared with the control sample, is indicative of a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD). Similarly, the presence of one or more different splicing

variants in the test sample, or the presence of significantly different amounts of different splicing variants in the test sample, as compared with the control sample, is indicative of a susceptibility to a disease or condition associated with a FLAP nucleic acid. Various means of examining expression or composition of the polypeptide encoded by a FLAP nucleic acid can be used, including:

5 spectroscopy, colorimetry, electrophoresis, isoelectric focusing and immunoassays (*e.g.*, David *et al.*, U.S. Pat. 4,376,110) such as immunoblotting (see also *Current Protocols in Molecular Biology*, particularly Chapter 10). For example, in one embodiment, an antibody capable of binding to the polypeptide

10 (*e.g.*, as described above), preferably an antibody with a detectable label, can be used. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a

15 detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

20 Western blotting analysis, using an antibody as described above that specifically binds to a polypeptide encoded by an altered FLAP (*e.g.*, by a FLAP having a SNP as shown in Table 13), or an antibody that specifically binds to a polypeptide encoded by a non-altered nucleic acid, or an antibody that specifically binds to a particular splicing variant encoded by a nucleic acid,

25 can be used to identify the presence in a test sample of a particular splicing variant or of a polypeptide encoded by a polymorphic or altered FLAP, or the absence in a test sample of a particular splicing variant or of a polypeptide encoded by a non-polymorphic or non-altered nucleic acid. The presence of a polypeptide encoded by a polymorphic or altered nucleic acid, or the absence of

30 a polypeptide encoded by a non-polymorphic or non-altered nucleic acid, is diagnostic for a susceptibility to a disease or condition associated with FLAP, as

is the presence (or absence) of particular splicing variants encoded by the FLAP nucleic acid.

In one embodiment of this method, the level or amount of polypeptide encoded by a FLAP nucleic acid in a test sample is compared with the level or amount of the polypeptide encoded by the FLAP in a control sample. A level or amount of the polypeptide in the test sample that is higher or lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the polypeptide encoded by the FLAP, and is diagnostic for a susceptibility to a disease or condition associated with that FLAP.

Alternatively, the composition of the polypeptide encoded by a FLAP nucleic acid in a test sample is compared with the composition of the polypeptide encoded by the FLAP in a control sample (*e.g.*, the presence of different splicing variants). A difference in the composition of the polypeptide in the test sample, as compared with the composition of the polypeptide in the control sample, is diagnostic for a susceptibility to a disease or condition associated with that FLAP. In another embodiment, both the level or amount and the composition of the polypeptide can be assessed in the test sample and in the control sample. A difference in the amount or level of the polypeptide in the test sample, compared to the control sample; a difference in composition in the test sample, compared to the control sample; or both a difference in the amount or level, and a difference in the composition, is indicative of a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI).

The invention further pertains to a method for the diagnosis and identification of susceptibility to myocardial infarction, ACS, stroke or PAOD in an individual, by identifying an at-risk haplotype in FLAP. In one embodiment, the at-risk haplotype is one which confers a significant risk of MI, ACS, stroke or PAOD. In one embodiment, significance associated with a haplotype is measured by an odds ratio. In a further embodiment, the significance is measured by a percentage. In one embodiment, a significant risk is measured as an odds ratio of at least about 1.2, including by not limited to: 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. In a further embodiment, an odds ratio

of at least 1.2 is significant. In a further embodiment, an odds ratio of at least about 1.5 is significant. In a further embodiment, a significant increase in risk is at least about 1.7 is significant. In a further embodiment, a significant increase in risk is at least about 20%, including but not limited to about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95, and 98%. In a further embodiment, a significant increase in risk is at least about 50%. In yet another embodiment, an at-risk haplotype has a p value < 0.05. It is understood however, that identifying whether a risk is medically significant may also depend on a variety of factors, including the specific disease, the haplotype, and often, environmental factors.

The invention also pertains to methods of diagnosing a susceptibility to myocardial infarction, ACS, stroke or PAOD in an individual, comprising screening for an at-risk haplotype in the FLAP nucleic acid that is more frequently present in an individual susceptible to myocardial infarction (affected), compared to the frequency of its presence in a healthy individual (control), wherein the presence of the haplotype is indicative of susceptibility to myocardial infarction. Standard techniques for genotyping for the presence of SNPs and/or microsatellite markers that are associated with myocardial infarction, ACS, stroke or PAOD can be used, such as fluorescent based techniques (Chen, *et al.*, *Genome Res.* 9, 492 (1999), PCR, LCR, Nested PCR and other techniques for nucleic acid amplification. In a preferred embodiment, the method comprises assessing in an individual the presence or frequency of SNPs and/or microsatellites in the FLAP nucleic acid that are associated with myocardial infarction, ACS, stroke or PAOD, wherein an excess or higher frequency of the SNPs and/or microsatellites compared to a healthy control individual is indicative that the individual is susceptible to myocardial infarction, ACS, stroke or PAOD. See Table 7 for SNPs that comprise haplotypes that can be used as screening tools. See also Table 13 that sets forth SNPs and markers for use as screening tools.

In one embodiment, the at-risk haplotype is characterized by the presence of polymorphism(s) represented in Table 13. For example, SG13S99, where the SNP can be a "C" or a "T"; SG13S25, where the SNP can be a "G" or

an "A"; SG13S377, where the SNP can be a "G" or an "A"; SG13S106, where the SNP can be a "G" or an "A"; SG13S114, where the SNP can be a "T" or an "A"; SG13S89, where the SNP can be a "G" or an "A"; SG13S30, where the SNP can be a "G" or a "T"; SG13S32, where the SNP can be a "C" or an "A";
5 SG13S42, where the SNP can be a "G" or an "A"; and SG13S35, where the SNP can be a "G" or an "A".

Kits (*e.g.*, reagent kits) useful in the methods of diagnosis comprise components useful in any of the methods described herein, including for example, hybridization probes or primers as described herein (*e.g.*, labeled
10 probes or primers), reagents for detection of labeled molecules, restriction enzymes (*e.g.*, for RFLP analysis), allele-specific oligonucleotides, antibodies which bind to altered or to non-altered (native) FLAP polypeptide, means for amplification of nucleic acids comprising a FLAP, or means for analyzing the nucleic acid sequence of a nucleic acid described herein, or for analyzing the
15 amino acid sequence of a polypeptide as described herein, etc. In one embodiment, a kit for diagnosing susceptibility to MI, ACS, stroke or PAOD can comprise primers for nucleic acid amplification of a region in the FLAP nucleic acid comprising an at-risk haplotype that is more frequently present in an individual having MI, ACS, stroke or PAOD or susceptible to MI, ACS,
20 stroke or PAOD. The primers can be designed using portions of the nucleic acids flanking SNPs that are indicative of MI. In a particularly preferred embodiment, the primers are designed to amplify regions of the FLAP nucleic acid associated with an at-risk haplotype for MI, ACS, stroke or PAOD, as shown in Table 7, or more particularly the haplotype defined by the following
25 SNP markers: In one embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S377, SG13S106, SG13S32 and SG13S35 at the 13q12-13 locus. In one particular embodiment, the presence of the alleles T, G, G, G, A and G at SG13S99, SG13S25, SG13S377, SG13S106, SG13S32 and SG13S35,
30 respectively (the B6 haplotype), is diagnostic of susceptibility to myocardial infarction, ACS, stroke or PAOD. In another embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD

comprises markers SG13S99, SG13S25, SG13S106, SG13S30 and SG13S42 at the 13q12-13 locus. In one particular embodiment, the presence of the alleles T, G, G, G and A at SG13S99, SG13S25, SG13S106, SG13S30 and SG13S42, respectively (the B5 haplotype), is diagnostic of susceptibility to myocardial infarction, ACS, stroke or PAOD. In a third embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S25, SG13S106, SG13S30 and SG13S42 at the 13q12-13 locus. In one particular embodiment, the presence of the alleles G, G, G and A at SG13S25, SG13S106, SG13S30 and SG13S42, respectively (the B4 haplotype), is diagnostic of susceptibility to myocardial infarction, ACS, stroke or PAOD. In a fourth embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S99, SG13S25, SG13S114, SG13S89 and SG13S32 at the 13q12-13 locus. In one particular embodiment, the presence of the alleles T, G, T, G and A at SG13S99, SG13S25, SG13S114, SG13S89 and SG13S32, respectively (the A5 haplotype), is diagnostic of susceptibility to myocardial infarction, ACS, stroke or PAOD. In a fifth embodiment, a haplotype associated with a susceptibility to myocardial infarction, ACS, stroke or PAOD comprises markers SG13S25, SG13S114, SG13S89 and SG13S32 at the 13q12-12 locus. In one particular embodiment, the presence of the alleles G, T, G and A at SG13S25, SG13S114, SG13S89 and SG13S32, respectively (the A4 haplotype), is diagnostic of susceptibility to myocardial infarction, ACS, stroke or PAOD.

SCREENING ASSAYS AND AGENTS IDENTIFIED THEREBY

The invention provides methods (also referred to herein as “screening assays”) for identifying the presence of a nucleotide that hybridizes to a nucleic acid of the invention, as well as for identifying the presence of a polypeptide encoded by a nucleic acid of the invention. In one embodiment, the presence (or absence) of a nucleic acid molecule of interest (*e.g.*, a nucleic acid that has significant homology with a nucleic acid of the invention) in a sample can be assessed by contacting the sample with a nucleic acid comprising a nucleic acid of the invention (*e.g.*, a nucleic acid having the sequence of one of SEQ ID

NOs: 1 or 3 or the complement thereof, or a nucleic acid encoding an amino acid having the sequence of SEQ ID NO: 2, or a fragment or variant of such nucleic acids), under stringent conditions as described above, and then assessing the sample for the presence (or absence) of hybridization. In a preferred
5 embodiment, high stringency conditions are conditions appropriate for selective hybridization. In another embodiment, a sample containing a nucleic acid molecule of interest is contacted with a nucleic acid containing a contiguous nucleic acid sequence (*e.g.*, a primer or a probe as described above) that is at least partially complementary to a part of the nucleic acid molecule of interest
10 (*e.g.*, a FLAP nucleic acid), and the contacted sample is assessed for the presence or absence of hybridization. In a preferred embodiment, the nucleic acid containing a contiguous nucleic acid sequence is completely complementary to a part of the nucleic acid molecule of interest.

In any of these embodiments, all or a portion of the nucleic acid of
15 interest can be subjected to amplification prior to performing the hybridization.

In another embodiment, the presence (or absence) of a polypeptide of interest, such as a polypeptide of the invention or a fragment or variant thereof, in a sample can be assessed by contacting the sample with an antibody that specifically hybridizes to the polypeptide of interest (*e.g.*, an antibody such as
20 those described above), and then assessing the sample for the presence (or absence) of binding of the antibody to the polypeptide of interest.

In another embodiment, the invention provides methods for identifying agents (*e.g.*, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or
25 ribozymes which alter (*e.g.*, increase or decrease) the activity of the polypeptides described herein, or which otherwise interact with the polypeptides herein. For example, such agents can be agents which bind to polypeptides described herein (*e.g.*, binding agent for members of the leukotriene pathway, such as FLAP binding agents); which have a stimulatory or inhibitory effect on,
30 for example, activity of polypeptides of the invention; or which change (*e.g.*, enhance or inhibit) the ability of the polypeptides of the invention to interact with members of the leukotriene pathway binding agents (*e.g.*, receptors or

other binding agents); or which alter posttranslational processing of the leukotriene pathway member polypeptide, such as a FLAP polypeptide (*e.g.*, agents that alter proteolytic processing to direct the polypeptide from where it is normally synthesized to another location in the cell, such as the cell surface; agents that alter proteolytic processing such that more polypeptide is released from the cell, etc.)

In one embodiment, the invention provides assays for screening candidate or test agents that bind to or modulate the activity of polypeptides described herein (or biologically active portion(s) thereof), as well as agents identifiable by the assays. Test agents can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the “one-bead one-compound” library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S., *Anticancer Drug Des.* 12:145 (1997)).

In one embodiment, to identify agents which alter the activity of a FLAP polypeptide, a cell, cell lysate, or solution containing or expressing a FLAP polypeptide (*e.g.*, SEQ ID NO: 2 or another splicing variant encoded by a FLAP nucleic acid, such as a nucleic acid comprising a SNP as shown in Table 13), or a fragment or derivative thereof (as described above), can be contacted with an agent to be tested; alternatively, the polypeptide can be contacted directly with the agent to be tested. The level (amount) of FLAP activity is assessed (*e.g.*, the level (amount) of FLAP activity is measured, either directly or indirectly), and is compared with the level of activity in a control (*i.e.*, the level of activity of the FLAP polypeptide or active fragment or derivative thereof in the absence of the agent to be tested). If the level of the activity in the presence of the agent differs, by an amount that is statistically significant, from the level of the activity in the absence of the agent, then the agent is an agent that alters the activity of a FLAP polypeptide. An increase in the level of FLAP activity in the

presence of the agent relative to the activity in the absence of the agent, indicates that the agent is an agent that enhances FLAP activity. Similarly, a decrease in the level of FLAP activity in the presence of the agent, relative to the activity in the absence of the agent, indicates that the agent is an agent that inhibits FLAP activity. In another embodiment, the level of activity of a FLAP polypeptide or derivative or fragment thereof in the presence of the agent to be tested, is compared with a control level that has previously been established. A statistically significant difference in the level of the activity in the presence of the agent from the control level indicates that the agent alters FLAP activity.

10 The present invention also relates to an assay for identifying agents which alter the expression of a FLAP nucleic acid (*e.g.*, antisense nucleic acids, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes; which alter (*e.g.*, increase or decrease) expression (*e.g.*, transcription or translation) of the nucleic acid or which otherwise interact with the nucleic acids described herein, as well as agents identifiable by the assays. For example, a solution containing a nucleic acid encoding a FLAP polypeptide (*e.g.*, a FLAP nucleic acid) can be contacted with an agent to be tested. The solution can comprise, for example, cells containing the nucleic acid or cell lysate containing the nucleic acid; alternatively, the solution can be another solution that comprises elements necessary for transcription/translation of the nucleic acid. Cells not suspended in solution can also be employed, if desired. The level and/or pattern of FLAP expression (*e.g.*, the level and/or pattern of mRNA or of protein expressed, such as the level and/or pattern of different splicing variants) is assessed, and is compared with the level and/or pattern of expression in a control (*i.e.*, the level and/or pattern of the FLAP expression in the absence of the agent to be tested). If the level and/or pattern in the presence of the agent differ, by an amount or in a manner that is statistically significant, from the level and/or pattern in the absence of the agent, then the agent is an agent that alters the expression of the FLAP nucleic acid. Enhancement of FLAP expression indicates that the agent is an activator of FLAP activity. Similarly, inhibition of FLAP expression indicates that the agent is a repressor of FLAP activity.

In another embodiment, the level and/or pattern of FLAP polypeptide(s) (*e.g.*, different splicing variants) in the presence of the agent to be tested, is compared with a control level and/or pattern that have previously been established. A level and/or pattern in the presence of the agent that differs from the control level and/or pattern by an amount or in a manner that is statistically significant indicates that the agent alters FLAP expression.

In another embodiment of the invention, agents which alter the expression of a FLAP nucleic acid or which otherwise interact with the nucleic acids described herein, can be identified using a cell, cell lysate, or solution containing a nucleic acid encoding the promoter region of the FLAP nucleic acid operably linked to a reporter gene. After contact with an agent to be tested, the level of expression of the reporter gene (*e.g.*, the level of mRNA or of protein expressed) is assessed, and is compared with the level of expression in a control (*i.e.*, the level of the expression of the reporter gene in the absence of the agent to be tested). If the level in the presence of the agent differs, by an amount or in a manner that is statistically significant, from the level in the absence of the agent, then the agent is an agent that alters the expression of the FLAP nucleic acid, as indicated by its ability to alter expression of a nucleic acid that is operably linked to the FLAP nucleic acid promoter.

Enhancement of the expression of the reporter indicates that the agent is an activator of FLAP expression. Similarly, inhibition of the expression of the reporter indicates that the agent is a repressor of FLAP expression. In another embodiment, the level of expression of the reporter in the presence of the test agent, is compared with a control level that has previously been established. A level in the presence of the agent that differs from the control level by an amount or in a manner that is statistically significant indicates that the agent alters expression.

Agents which alter the amounts of different splicing variants encoded by a FLAP nucleic acid (*e.g.*, an agent which enhances expression of a first splicing variant, and which inhibits expression of a second splicing variant), as well as agents which stimulate activity of a first splicing variant and inhibit

activity of a second splicing variant, can easily be identified using these methods described above.

In other embodiments of the invention, assays can be used to assess the impact of a test agent on the activity of a polypeptide relative to a FLAP binding agent. For example, a cell that expresses a compound that interacts with a FLAP nucleic acid (herein referred to as a “FLAP binding agent”, which can be a polypeptide or other molecule that interacts with a FLAP nucleic acid, such as a receptor, or another molecule, such as 5-LO) is contacted with a FLAP in the presence of a test agent, and the ability of the test agent to alter the interaction between the FLAP and the FLAP binding agent is determined. Alternatively, a cell lysate or a solution containing the FLAP binding agent, can be used. An agent which binds to the FLAP or the FLAP binding agent can alter the interaction by interfering with, or enhancing the ability of the FLAP to bind to, associate with, or otherwise interact with the FLAP binding agent. Determining the ability of the test agent to bind to a FLAP nucleic acid or a FLAP nucleic acid binding agent can be accomplished, for example, by coupling the test agent with a radioisotope or enzymatic label such that binding of the test agent to the polypeptide can be determined by detecting the labeled with ^{125}I , ^{35}S , ^{14}C or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Alternatively, test agents can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. It is also within the scope of this invention to determine the ability of a test agent to interact with the polypeptide without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a test agent with a FLAP or a FLAP binding agent without the labeling of either the test agent, FLAP, or the FLAP binding agent. McConnell, H.M. *et al.*, *Science* 257:1906-1912 (1992). As used herein, a “microphysiometer” (*e.g.*, Cytosensor™) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-

addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between ligand and polypeptide.

Thus, these receptors can be used to screen for compounds that are agonists for use in treating a disease or condition associated with FLAP or a
5 susceptibility to a disease or condition associated with FLAP, or antagonists for studying a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI, ACS, stroke or PAOD). Drugs can be designed to regulate FLAP activation, that in turn can be used to regulate signaling pathways and transcription events of genes downstream or of proteins or polypeptides
10 interacting with FLAP (*e.g.*, 5-LO).

In another embodiment of the invention, assays can be used to identify polypeptides that interact with one or more FLAP polypeptides, as described herein. For example, a yeast two-hybrid system such as that described by Fields and Song (Fields, S. and Song, O., *Nature* 340:245-246 (1989)) can be used to
15 identify polypeptides that interact with one or more FLAP polypeptides. In such a yeast two-hybrid system, vectors are constructed based on the flexibility of a transcription factor that has two functional domains (a DNA binding domain and a transcription activation domain). If the two domains are separated but fused to two different proteins that interact with one another,
20 transcriptional activation can be achieved, and transcription of specific markers (*e.g.*, nutritional markers such as His and Ade, or color markers such as lacZ) can be used to identify the presence of interaction and transcriptional activation. For example, in the methods of the invention, a first vector is used which includes a nucleic acid encoding a DNA binding domain and also a FLAP
25 polypeptide, splicing variant, or fragment or derivative thereof, and a second vector is used which includes a nucleic acid encoding a transcription activation domain and also a nucleic acid encoding a polypeptide which potentially may interact with the FLAP polypeptide, splicing variant, or fragment or derivative thereof (*e.g.*, a FLAP polypeptide binding agent or receptor). Incubation of
30 yeast containing the first vector and the second vector under appropriate conditions (*e.g.*, mating conditions such as used in the Matchmaker™ system from Clontech (Palo Alto, California, USA)) allows identification of colonies

that express the markers of interest. These colonies can be examined to identify the polypeptide(s) that interact with the FLAP polypeptide or fragment or derivative thereof. Such polypeptides may be useful as agents that alter the activity of expression of a FLAP polypeptide, as described above.

5 In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either the FLAP, the FLAP binding agent, or other components of the assay on a solid support, in order to facilitate separation of complexed from uncomplexed forms of one or both of the polypeptides, as well as to accommodate automation of the assay. Binding of a
10 test agent to the polypeptide, or interaction of the polypeptide with a binding agent in the presence and absence of a test agent, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein (*e.g.*, a glutathione-S-transferase fusion protein) can be provided
15 which adds a domain that allows a FLAP nucleic acid or a FLAP binding agent to be bound to a matrix or other solid support.

 In another embodiment, modulators of expression of nucleic acid molecules of the invention are identified in a method wherein a cell, cell lysate, or solution containing a nucleic acid encoding a FLAP nucleic acid is contacted
20 with a test agent and the expression of appropriate mRNA or polypeptide (*e.g.*, splicing variant(s)) in the cell, cell lysate, or solution, is determined. The level of expression of appropriate mRNA or polypeptide(s) in the presence of the test agent is compared to the level of expression of mRNA or polypeptide(s) in the absence of the test agent. The test agent can then be identified as a modulator
25 of expression based on this comparison. For example, when expression of mRNA or polypeptide is greater (statistically significantly greater) in the presence of the test agent than in its absence, the test agent is identified as a stimulator or enhancer of the mRNA or polypeptide expression. Alternatively, when expression of the mRNA or polypeptide is less (statistically significantly
30 less) in the presence of the test agent than in its absence, the test agent is identified as an inhibitor of the mRNA or polypeptide expression. The level of

mRNA or polypeptide expression in the cells can be determined by methods described herein for detecting mRNA or polypeptide.

In yet another embodiment, the invention provides methods for identifying agents (*e.g.*, fusion proteins, polypeptides, peptidomimetics, 5 prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) which alter (*e.g.*, increase or decrease) the activity of a member of leukotriene pathway binding agent, such as a FLAP binding agent (*e.g.*, 5-LO), as described herein. For example, such agents can be agents which have a stimulatory or inhibitory effect on, for example, the activity of a member of 10 leukotriene pathway binding agent, such as a FLAP binding agent; which change (*e.g.*, enhance or inhibit) the ability a member of leukotriene pathway binding agents, (*e.g.*, receptors or other binding agents) to interact with the polypeptides of the invention; or which alter posttranslational processing of the member of leukotriene pathway binding agent, (*e.g.*, agents that alter proteolytic 15 processing to direct the member of the leukotriene pathway binding agent from where it is normally synthesized to another location in the cell, such as the cell surface; agents that alter proteolytic processing such that more active binding agent is released from the cell, etc.).

For example, the invention provides assays for screening candidate or 20 test agents that bind to or modulate the activity of a member of the leukotriene pathway (or enzymatically active portion(s) thereof), as well as agents identifiable by the assays. As described above, test agents can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid 25 phase or solution phase libraries; synthetic library methods requiring deconvolution; the “one-bead one-compound” library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of 30 compounds (Lam, K.S. *Anticancer Drug Des.*, 12:145 (1997)).

In one embodiment, to identify agents which alter the activity of a member of the leukotriene pathway (such as a FLAP binding agent, or an agent

which binds to a member of the leukotriene pathway (a “binding agent”), a cell, cell lysate, or solution containing or expressing a binding agent (*e.g.*, 5-LO, or a leukotriene pathway member receptor, or other binding agent), or a fragment (*e.g.*, an enzymatically active fragment) or derivative thereof, can be contacted with an agent to be tested; alternatively, the binding agent (or fragment or derivative thereof) can be contacted directly with the agent to be tested. The level (amount) of binding agent activity is assessed (either directly or indirectly), and is compared with the level of activity in a control (*i.e.*, the level of activity in the absence of the agent to be tested). If the level of the activity in the presence of the agent differs, by an amount that is statistically significant, from the level of the activity in the absence of the agent, then the agent is an agent that alters the activity of the member of the leukotriene pathway. An increase in the level of the activity relative to a control, indicates that the agent is an agent that enhances (is an agonist of) the activity. Similarly, a decrease in the level of activity relative to a control, indicates that the agent is an agent that inhibits (is an antagonist of) the activity. In another embodiment, the level of activity in the presence of the agent to be tested, is compared with a control level that has previously been established. A level of the activity in the presence of the agent that differs from the control level by an amount that is statistically significant indicates that the agent alters the activity.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a test agent that is a modulating agent, an antisense nucleic acid molecule, a specific antibody, or a polypeptide-binding agent) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent.

Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein. In addition, an agent identified as described herein can be used to alter activity of a

polypeptide encoded by a FLAP nucleic acid, or to alter expression of a FLAP nucleic acid, by contacting the polypeptide or the nucleic acid (or contacting a cell comprising the polypeptide or the nucleic acid) with the agent identified as described herein.

5

The present invention is now illustrated by the following Examples, which are not intended to be limiting in any way. The teachings of all references cited are incorporated herein in their entirety.

EXAMPLE 1: IDENTIFICATION OF GENE AND HAPLOTYPES ASSOCIATED WITH MI

5 A genome wide scan of 296 multiplex Icelandic families with 713 MI
patients was performed. Through the suggestive linkage to a locus on
chromosome 13q12-13 for female MI patients and early onset MI patients, and
haplotype association analysis, the gene encoding the 5-lipoxygenase activating
protein (FLAP) was identified, and a 4-SNP haplotype within the gene was
10 determined to confer a near 2-fold risk of MI. Male patients showed strongest
association to the at-risk haplotype. Independent confirmation of FLAP
association to MI was obtained in a British cohort of patients with sporadic MI.
These findings support FLAP as the first specific gene isolated that confers
substantial risk of the complex trait of MI.

15

METHODS

Study population

Patients entering the study were recruited from a registry that includes
5 all MIs that occurred before the age of 75 (over 8,000 patients) in Iceland from
1981 to 2000. This registry is a part of the World Health Organization
MONICA Project (The World Health Organization MONICA Project, WHO
MONICA Project Principal Investigators, *J Clin Epidemiol* **41**, 105-14 (1988)).
Diagnoses of all patients in the registry followed strict diagnostic rules based on
10 signs, symptoms, electrocardiograms, cardiac enzymes, and necropsy findings.

Genotypes from 713 MI patients and 1741 of their first-degree relatives
were used in the linkage analysis. For the microsatellite association study of the
MI locus, 802 unrelated MI patients (n=233 females, n=624 males and n= 302
early onset) and 837 population-based controls were used. For the SNP
15 association study in and around the FLAP gene 779 unrelated MI patients were
genotyped (n=293 females, n=486 males and n=358 early onset). The control
group for the SNP association study was population based and comprised of 628
unrelated males and females in the age range of 30-85 years whose medical
history was unknown.

20 The study was approved by the Data Protection Commission of Iceland
and the National Bioethics Committee of Iceland. Informed consent was
obtained from all study participants. Personal identifiers associated with
medical information and blood samples were encrypted with a third party
encryption system as previously described (Gulcher, J.R., Kristjansson, K.,
25 Gudbjartsson, H. & Stefansson, K., *Eur J Hum Genet* **8**, 739-42 (2000)).

Statistical analysis

A genome-wide scan was performed as previously described
(Gretarsdottir, S. *et al. Am J Hum Genet* **70**, 593-603 (2002)), using a set of
30 approximately 1000 microsatellite markers. Multipoint, affected-only allele-
sharing methods (Kong, A. & Cox, N.J., *Am J Hum Genet* **61**, 1179-88 (1997))
were used to assess the evidence for linkage. All results were obtained using

the program Allegro (Gudbjartsson, D.F., Jonasson, K., Frigge, M.L. & Kong, A. Allegro, *Nat Genet* 25, 12-3 (2000)) and the deCODE genetic map (Kong, A. *et al.*, *Nat Genet* 31, 241-7 (2002)). The S_{pairs} scoring function (Whittemore, A.S. & Halpern, J., *Biometrics* 50, 118-27 (1994); Kruglyak, L., Daly, M.J.,
 5 Reeve-Daly, M.P. & Lander, E.S., *Am J Hum Genet* 58, 1347-63 (1996)) was used, as was the exponential allele-sharing model (Kong, A. & Cox, N.J. *Am J Hum Genet* 61, 1179-88 (1997)) to generate the relevant 1-df (degree of freedom) statistics. When combining the family scores to obtain an overall score, a weighting scheme was used that is halfway on a log scale between
 10 weighting each affected pair equally and weighting each family equally. In the analysis, all genotyped individuals who are not affected are treated as “unknown”. Because of concern with small sample behaviour, corresponding P values were usually computed in two different ways for comparison, and the less significant one was reported. The first P value is computed based on large
 15 sample theory; $Z_{\text{lr}} = \sqrt{(2 \log_e (10) \text{ LOD})}$ and is distributed approximately as a standard normal distribution under the null hypothesis of no linkage (Kong, A. & Cox, N.J. *Am J Hum Genet* 61, 1179-88 (1997)). A second P value is computed by comparing the observed LOD score to its complete data sampling distribution under the null hypothesis (Gudbjartsson, D.F., Jonasson, K., Frigge,
 20 M.L. & Kong, A. Allegro, *Nat Genet* 25, 12-3 (2000)). When a data set consists of more than a handful of families, these two P values tend to be very similar. The information measure that was used (Nicolae, D. University of Chicago (1999)), and is implemented in Allegro, is closely related to a classical measure of information (Dempster, A., Laird, NM, Rubin, DB., *J R Stat Soc B*
 25 39, 1-38 (1977) and has a property that is between 0, if the marker genotypes are completely uninformative, and 1, if the genotypes determine the exact amount of allele sharing by descent among the affected relatives.

For single-marker association studies, Fisher’s exact test was used to calculate two-sided P values for each allele. All P values were unadjusted for
 30 multiple comparisons unless specifically indicated. Allelic rather than carrier frequencies were presented for microsatellites, SNPs and haplotypes. To minimize any bias due to the relatedness of the patients that were recruited as

families for the linkage analysis first and second-degree relatives were eliminated from the patient list. For the haplotype analysis, the program NEMO was used (Gretarsdottir, S. *et al.*, *Nat Genet* **35**, 131-8 (2003)), which handles missing genotypes and uncertainty with phase through a likelihood procedure, using the expectation-maximization algorithm as a computational tool to estimate haplotype frequencies. Under the null hypothesis, the affected individuals and controls are assumed to have identical haplotype frequencies. Under the alternative hypotheses, the candidate at-risk haplotype is allowed to have a higher frequency in the affected individuals than in controls, while the ratios of frequencies of all other haplotypes are assumed to be the same in both groups. Likelihoods are maximized separately under both hypotheses, and a corresponding 1-df likelihood ratio statistic used to evaluate statistical significance (*id*). Even though searches were only performed for haplotypes that increase the risk, all reported P values are two-sided unless otherwise stated. To assess the significance of the haplotype association corrected for multiple testing, a randomisation test was carried out using the same genotype data. The cohorts of affected individuals and controls were randomized, and the analysis was repeated. This procedure was repeated up to 1.000 times and the P value presented is the fraction of replications that produced a P value for a haplotype tested that is lower than or equal to the P value observed using the original patient and control cohorts.

For both single-marker and haplotype analysis, relative risk (RR) and population attributable risk was calculated assuming a multiplicative model (Terwilliger, J.D. & Ott, J. A., *Hum Hered* **42**, 337-46 (1992); Falk, C.T. & Rubinstein, P., *Ann Hum Genet* **51** (Pt 3), 227-33 (1987)) in which the risk of the two alleles of haplotypes a person carries multiply. LD was calculated between pairs of SNPs using the standard definition of D' (Lewontin, R.C., *Genetics* **50**, 757-82 (1964)) and R^2 (Hill, W.G. & Robertson, A., *Genetics* **60**, 615-28 (1968)). Using NEMO, frequencies of the two marker allele combinations are estimated by maximum likelihood, and deviation from linkage equilibrium is evaluated by a likelihood ratio test. When plotting all SNP combinations to elucidate the LD structure in a particular region, D' was plotted

in the upper left corner and the P value in the lower right corner. In the LD plots presented, the markers are plotted equidistantly rather than according to their physical positions.

5 *Identification of DNA polymorphisms.*

New polymorphic repeats (e.g., dinucleotide or trinucleotide repeats) were identified with the Sputnik program. For microsatellite alleles: the CEPH sample 1347-02 (Centre d'Etudes du Polymorphisme Humain, genomics repository) is used as a reference. The lower allele of each microsatellite in this sample is set at 0 and all other alleles in other samples are numbered according
10 in relation to this reference. Thus allele1 is 1 bp longer than the lower allele in the CEPH sample, allele 2 is 2 bp longer than the lower allele in the CEPH sample, allele 3 is 3 bp longer than the lower allele in the CEPH sample, allele 4 is 4 bp longer than the lower allele in the CEPH sample, allele -1 is 1 bp shorter
15 than the lower allele in the CEPH sample , allele -2 is 2 bp shorter than the lower allele in the CEPH sample, and so on. Single nucleotide polymorphisms in the gene were detected by PCR sequencing exonic and intronic regions from patients and controls. Public single nucleotide polymorphisms were obtained from the NCBI SNP database. SNPs were genotyped using a method for
20 detecting SNPs with fluorescent polarization template-directed dye-terminator incorporation (SNP-FP-TDI assay) (Chen, X., Zehnbaauer, B., Gnirke, A. & Kwok, P.Y., *Proc Natl Acad Sci U S A* 94, 10756-61. (1997)) and TaqMan assays (Applied Biosystems).

25 RESULTS

Linkage analysis

A genome wide scan was performed in search of MI susceptibility genes using a framework set of around 1000 microsatellite markers. The initial
30 linkage analysis included 713 MI patients who fulfilled the WHO MONICA research criteria (The World Health Organization MONICA Project, WHO MONICA Project Principal Investigators,. *J Clin Epidemiol* 41, 105-14 (1988))

and were clustered in 296 extended families. The linkage analysis was also repeated for early onset, male and female patients separately. Description of the number of patients and families in each analysis are provided in Table 1.

5

TABLE 1: Number of patients that cluster into families and the corresponding number of families used in the linkage analysis

Phenotype	Number of patients	Number of families	Number of pairs	Genotyped relatives ^a
All MI patients	713	296	863	1741
Males	575	248	724	1385
Females	140	56	108	366
Early onset	194	93	156	739

^aGenotyped relatives were used to increase the information on IBD sharing among the patients in the linkage analysis

None of these analyses yielded a locus of genome-wide significance. However, the most promising LOD score (LOD = 2.86) was observed on chromosome 13q12-13
10 for female MI patients at the peak marker D13S289 (data not shown). This locus also had the most promising LOD score (LOD = 2.03) for patients with early onset MI. After increasing the information on identity-by-descent sharing to over 90% by typing 14 additional microsatellite markers in a 30 centiMorgan (cM) region around D13S289, the LOD score from the female analysis dropped to 2.48 (P value = 0.00036), while the
15 highest LOD score remained at D13S289 (FIG. 9.1).

Microsatellite association study

The 7.6 Mb region that corresponds to a drop of one in LOD score in the female MI linkage analysis, contains 40 known genes (Table 2).

20

Table 2: Genes residing within the one LOD drop region of the chromosome 13q12-13 linkage peak.

LL_Symbol	LL_gene_name
USP12L1	ubiquitin specific protease 12 like 1
RPL21	ribosomal protein L21
GTF3A	general transcription factor IIIA

MTIF3	mitochondrial translational initiation factor 3
PDZRN1	PDZ domain containing ring finger 1
MGC9850	hypothetical protein MGC9850
POLR1D	polymerase (RNA) I polypeptide D, 16kDa
GSH1	GS homeobox 1
IPF1	insulin promoter factor 1, homeodomain transcription factor
CDX2	caudal type homeo box transcription factor 2
FLT3	fms-related tyrosine kinase 3
LOC255967	hypothetical protein LOC255967
	fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)
FLT1	
C13orf12	chromosome 13 open reading frame 12
LOC283537	hypothetical protein LOC283537
KIAA0774	KIAA0774 protein
	solute carrier family 7 (cationic amino acid transporter, y+ system), member 1
SLC7A1	
UBL3	ubiquitin-like 3
MGC2599	hypothetical protein MGC2599 similar to katanin p60 subunit A 1 2599
HMGB1	high-mobility group box 1
D13S106E	highly charged protein
ALOX5AP	arachidonate 5-lipoxygenase-activating protein
FLJ14834	hypothetical protein FLJ14834
MGC40178	hypothetical protein MGC40178
HSPH1	heat shock 105kDa/110kDa protein 1
B3GTL	beta 3-glycosyltransferase-like
	similar to G protein coupled receptor affecting testicular descent (H. sapiens)
GREAT	
LOC196549	similar to hypothetical protein FLJ20897
13CDNA73	hypothetical protein CG003
BRCA2	breast cancer 2, early onset
CG018	hypothetical gene CG018
PRO0297	PRO0297 protein
LOC88523	CG016
CG012	hypothetical gene CG012
CG030	hypothetical gene CG030
CG005	hypothetical protein from BCRA2 region
APRIN	androgen-induced proliferation inhibitor
KL	Klotho
STARD13	START domain containing 13
RFC3	replication factor C (activator 1) 3, 38kDa

To determine which gene in this region most likely contributes to MI, 120 microsatellite markers positioned within this region were typed, and a case-control

association study was performed using 802 unrelated MI patients and 837 population-based controls. The association study was also repeated for each of the three phenotypes that were used in the linkage study, i.e. early onset, male and female MI patients.

5 The initial association analysis was performed when the average spacing between microsatellite markers was approximately 100 kb. This analysis revealed several extended haplotypes composed of 4 and 5 microsatellite markers that were significantly associated with female MI (see FIGs 1 and 2, and Tables 13 and 14). A region common to all these extended haplotypes, is defined by markers DG13S166
10 and D13S1238. This region included only one gene, the FLAP nucleic acid sequence. The two marker haplotype involving alleles 0 and -2 for markers DG13S166 and D13S1238, respectively, was found in excess in patients.

This was the first evidence that the FLAP gene might be involved in the pathogenesis of myocardial infarction.

15 Subsequent haplotype analysis that included more microsatellite markers (n=120) in the candidate region on chromosome 13q12-13, now with a marker density of 1 microsatellite marker per 60 kb, showed decreased significance of the original haplotype association. However, the haplotype association analysis using increased density of markers again pointed towards the FLAP gene. This analysis strongly
20 suggested that a 300 kb region was involved in the susceptibility of myocardial infarction. As shown in FIG. 7.2, the haplotype that showed association to all MI with the lowest P value (0.00009) covered a region that contains 2 known genes, including the gene encoding arachidonate 5-lipoxygenase-activating protein (FLAP) and a gene with an unknown function called highly charged protein. However, the haplotype
25 association to female MI in this region was less significant (P value =0.005) than for all MI patients and to our surprise, the most significant haplotype association was observed for male MI patients (P value = 0.000002). This male MI haplotype was the only haplotype that remained significant after adjusting for all haplotypes tested.

In view of the association results described above, FLAP was an attractive
30 candidate and therefore efforts were focused on this gene.

Screening for polymorphisms in FLAP and linkage disequilibrium mapping

To determine whether variations within the FLAP gene significantly associate with MI and to search for causal variations, the FLAP gene was sequenced in 93 patients and 93 controls. The sequenced region covers 60 kb containing the FLAP gene, including the 5 known exons and introns and the 26 kb region 5' to the first exon and 7 kb region 3' to the fifth exon. In all, 144 SNPs were identified, of those 96 were excluded from further analysis either because of low minor allele frequency or they were completely correlated with other SNPs and thus redundant. FIG. 9 shows the distribution of the 48 SNPs, used for genotyping, relative to exons, introns and the 5' and 3' flanking regions of the FLAP gene. Only one SNP was identified within a coding sequence (exon 2). This SNP did not lead to amino acid substitution. The locations of these SNPs in the NCBI human genome assembly, build 34, are listed in Table 3.

Table 3: Locations of all genotyped SNPs in NCBI build 34 of the human genome assembly

SNP name	Build34 start
SG13S381	29083350
SG13S366	29083518
SG13S1	29086224
SG13S2	29087473
SG13S367	29088090
SG13S10	29088473
SG13S3	29089044
SG13S368	29089886
SG13S4	29090997
SG13S5	29091307
SG13S90	29091780
SG13S6	29092536
SG13S371	29093964
SG13S372	29094259
SG13S373	29096688
SG13S375	29096874
SG13S376	29096962
SG13S25	29097553
SG13S377	29101965
SG13S100	29104271
SG13S95	29106329
SG13S191	29107830
SG13S106	29108579

SG13S114	29110096
SG13S121	29112174
SG13S122	29112264
SG13S43	29112455
SG13S192	29116308
SG13S88	29116401
SG13S137	29118118
SG13S86	29118815
SG13S87	29118873
SG13S39	29119740
SG13S26	29122253
SG13S27	29122283
SG13S29	29123643
SG13S89	29124441
SG13S96	29124906
SG13S30	29125840
SG13S97	29129139
SG13S32	29130547
SG13S41	29134045
SG13S42	29135877
SG13S34	29137100
SG13S35	29138117
SG13S181	29138633
SG13S184	29139435
SG13S188	29140805

In addition to the SNPs, a polymorphism consisting of a monopolymer A repeat that has been described in the FLAP promoter region was typed (Koshino, T. *et al.*, 5 *Mol Cell Biol Res Commun* 2, 32-5 (1999)).

The linkage disequilibrium (LD) block structure defined by the 48 SNPs that were selected for further genotyping is shown in FIG. 11. A strong LD was detected across the FLAP region, although it appears that at least one recombination may have occurred dividing the region into two strongly correlated LD blocks.

10 *Haplotype association to MI*

To perform a case-control association study the 48 selected SNPs and the monopolymer A repeat marker were genotyped in a set of 779 unrelated MI patients and 628 population-based controls. Each of the 49 markers were tested individually for association to the disease. Three SNPs, one located 3 kb upstream of the first exon and

the other two 1 and 3 kb downstream of the first exon, showed nominally significant association to MI (Table 4).

Table 4: SNP allelic association in the MI cohort

Phenotype	Marker	Allele	<i>P</i> value	RR	# Pat.	% Pat.	# Ctrl	% Ctrl
All patients	SG13S106	G	0.0044	1.29	681	72.0	530	66.6
	SG13S100	A	0.020	1.29	388	69.6	377	63.9
	SG13S114	T	0.021	1.21	764	70.0	602	65.8
Males	SG13S106	G	0.0037	1.35	422	72.9	530	66.6
	SG13S100	A	0.0099	1.36	292	70.7	377	63.9
	SG13S114	T	0.026	1.24	477	70.4	602	65.8
Early onset	SG13S100	A	0.0440	1.43	99	71.7	377	63.9

Nominally significant SNP association with corresponding number of patients

5 (# Pat.) and controls (#Ctrl). RR refers to relative risk.

However, after adjusting for the number of markers tested, these results were not significant. A search was then conducted for haplotypes that show association to the disease using the same cohorts. For computational reasons, the search was limited
 10 to haplotype combinations constructed out of two, three or four SNPs and only haplotypes that were in excess in the patients were tested. The resulting *P* values were adjusted for all the haplotypes tested by randomizing the patients and controls (see Methods).

Several haplotypes were found that were significantly associated to the disease
 15 with an adjusted *P* value less than 0.05 (Table 5).

TABLE 5: SNP haplotypes that significantly associate with Icelandic MI patients

SG13S4	SG13S6	SG13S372	SG13S25	SG13S377	SG13S100	SG13S95	SG13S114	SG13S192	SG13S137	SG13S86	SG13S87	SG13S39	SG13S27	SG13S89	SG13S96	SG13S32	SG13S41	SG13S42	SG13S34	SG13S188	<i>P</i> value ^a	<i>P</i> value ^b	Pat.fr q	Ctrl.fr q	RR	D' ^c
			G				T							G		A					0,0000023	0,005	0,158	0,095	1,80	1,00
			G				T			A						A					0,0000030	0,006	0,158	0,095	1,78	1,00
			G				T									A			T		0,0000032	0,007	0,157	0,094	1,79	1,00
			G		A					A						A					0,0000046	0,012	0,158	0,083	2,07	0,89
			G			T	T									A					0,0000047	0,012	0,154	0,093	1,78	1,00
			G				T			G						A					0,0000055	0,015	0,147	0,087	1,81	1,00
			G		A											A			T		0,0000061	0,017	0,157	0,083	2,07	0,89
			G		A									G		A					0,0000063	0,017	0,157	0,084	2,04	0,89
			G				T									A					0,0000070	0,021	0,157	0,096	1,76	1,00
			G				T								A	A					0,0000075	0,022	0,149	0,089	1,78	1,00
	G					T	T									A					0,0000083	0,024	0,208	0,139	1,62	0,99
			G		A					G						A					0,0000084	0,026	0,145	0,074	2,14	0,88
			G				T	A								A					0,0000084	0,026	0,139	0,082	1,82	1,00
			G				T						G			A					0,0000091	0,028	0,156	0,096	1,75	1,00
	G						T									A			T		0,0000094	0,028	0,210	0,141	1,61	0,99
	G		G				T									A					0,0000100	0,028	0,156	0,096	1,74	1,00
	G				A											A			A		0,0000101	0,028	0,215	0,133	1,80	0,81
			G		A											A					0,0000105	0,028	0,157	0,084	2,03	0,89
	G				A					A						A					0,0000108	0,029	0,214	0,133	1,78	0,81
			G		A										A	A					0,0000110	0,030	0,146	0,075	2,10	0,88
	G						T			A						A					0,0000112	0,030	0,212	0,144	1,60	1,00
			G		A			A											T		0,0000113	0,030	0,151	0,081	2,03	0,78
			G				T						G			A					0,0000118	0,031	0,156	0,096	1,73	1,00
	G				A											A			T		0,0000126	0,034	0,212	0,131	1,79	0,79
	G						T							G		A					0,0000129	0,035	0,211	0,144	1,59	1,00
			G		A								G			A					0,0000134	0,035	0,156	0,084	2,01	0,89
	G						T									A					0,0000136	0,036	0,211	0,143	1,60	1,00
	G		G		A											A					0,0000137	0,036	0,156	0,085	2,00	0,89
			G		A			A							A						0,0000148	0,037	0,151	0,081	2,01	0,78
			G				T	A											T		0,0000150	0,037	0,160	0,099	1,73	0,87
			G		A			A								A					0,0000150	0,037	0,130	0,066	2,13	0,90
			G				T		C										T		0,0000154	0,039	0,152	0,094	1,73	0,93
			G				T									A		A			0,0000154	0,040	0,155	0,097	1,70	1,00
			G				T		C							A					0,0000157	0,040	0,141	0,085	1,76	1,00
			G	G	A											A					0,0000158	0,040	0,152	0,084	1,94	0,90
	G						T						G			A					0,0000163	0,040	0,210	0,143	1,59	0,99
	G						T			G						A					0,0000166	0,041	0,200	0,134	1,61	0,92
	G				A									G		A					0,0000168	0,042	0,213	0,133	1,76	0,81

		G	A						G			A				0,0000168	0,042	0,156	0,084	2,00	0,89
C	G		A									A				0,0000171	0,042	0,211	0,136	1,70	0,81
	G				T	A						A				0,0000183	0,043	0,192	0,128	1,62	0,85
	G		A									A				0,0000184	0,043	0,212	0,132	1,77	0,81
	G				T							A		T		0,0000193	0,046	0,328	0,251	1,46	0,99
		G			T				G					T		0,0000194	0,046	0,175	0,115	1,64	0,98
	G	G		A								A				0,0000202	0,048	0,210	0,136	1,70	0,81
	G		G	A		A										0,0000209	0,049	0,151	0,082	2,00	0,76

^a Single test P values. ^b P values adjusted for all the SNP haplotypes tested.

^c Measure of correlation with Haplotype A4 .

The most significant association was observed for a four SNP haplotype spanning 33 kb, including the first four exons of the gene (Fig. 9.3), with a nominal *P* value of 0.0000023 and an adjusted *P* value of 0.005. This haplotype, labelled A4, has a haplotype frequency of 15.8% (carrier frequency 30.3%) in patients versus 9.5% (carrier frequency 17.9%) in controls (Table 6).

Table 6: Association of the A4 haplotype to MI, Stroke and PAOD

Phenotype (n)	Frq. Pat.	RR	PAR	<i>P</i> -value	<i>P</i> -value ^a
<i>MI</i> (779)	0.158	1.80	0.135	0.0000023	0.005
Males (486)	0.169	1.95	0.158	0.00000091	ND ^b
Females (293)	0.138	1.53	0.094	0.0098	ND
Early onset (358)	0.138	1.53	0.094	0.0058	ND
<i>Stroke</i> (702) ^c	0.149	1.67	0.116	0.000095	ND
Males (373)	0.156	1.76	0.131	0.00018	ND
Females (329)	0.141	1.55	0.098	0.0074	ND
<i>PAOD</i> (577) ^c	0.122	1.31	0.056	0.061	ND
Males (356)	0.126	1.36	0.065	0.057	ND
Females (221)	0.114	1.22	0.041	0.31	ND

^a *P* value adjusted for the number of haplotypes tested. ^bNot done. ^cExcluding known cases of MI. Shown is the FLAP A4 haplotype and corresponding number of patients (n), haplotype frequency in patients (Frq. pat.), relative risk (RR), population attributed risk (PAR) and *P* values. The A4 haplotype is defined by the following SNPs: SG13S25, SG13S114, SG13S89 and SG13S32 (Table 5). The same controls (n=628) are used for the association analysis in MI, stroke and PAOD as well as for the male, female and early onset analysis. The A4 haplotype frequency in the control cohort is 0.095.

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The relative risk conferred by The A4 haplotype compared to other haplotypes constructed out of the same SNPs, assuming a multiplicative model, was 1.8 and the corresponding population attributable risk (PAR) was 13.5%. As shown in Table 6, the A4 haplotype was observed in higher frequency in male patients (carrier frequency

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30.9%) than in female patients (carrier frequency 25.7%). All the other haplotypes that were significantly associated with an adjusted P value less than 0.05, were highly correlated with the A4 haplotype and should be considered variants of that haplotype (Table 5). Table 6 shows the results of the haplotype A4 association study using 779
 5 MI patients, 702 stroke patients, 577 PAOD patients and 628 controls. First and second degree relatives were excluded from the patient cohorts. All known cases of MI were removed from the stroke and PAOD cohorts before testing for association. A significant association of the A4 haplotype to stroke was observed, with a relative risk of 1.67 (P value = 0.000095). In addition, it was determined whether the A4 haplotype
 10 was primarily associated with a particular sub-phenotype of stroke, and found that both ischemic and hemorrhagic stroke were significantly associated with the A4 haplotype (Table 22, below).

More variants of haplotype A4

15 Two correlated series of SNP haplotypes were observed in excess in patients, denoted as A and B in Table 7. The length of the haplotypes varies between 33 and 69 Kb, and the haplotypes cover one or two blocks of linkage disequilibrium. Both series of haplotypes contain the common allele G of the SNP SG13S25. All haplotypes in the A series contain the SNP SG13S114, while all haplotypes in the B series contain the
 20 SNP SG13S106. In the B series, the haplotypes B4, B5, and B6 have a relative risk (RR) greater than 2 and with allelic frequencies above 10%. The haplotypes in A series have slightly lower RR and lower p-values, but higher frequency (15-16%). The haplotypes in series B and A are strongly correlated, i.e. the haplotypes in B define a subset of the haplotypes in A. Hence, haplotypes B are more specific than A.
 25 Haplotypes A are however more sensitive, i.e. they capture more individuals with the putative mutation, as is observed in the population attributable risk which is less for B than for A. Furthermore, these haplotypes show similar risk ratios and allelic frequency for early-onset patients (defined as onset of first MI before the age of 55) and for both gender. In addition, analyzing various groups of patients with known risk
 30 factors, such as hypertension, high cholesterol, smoking and diabetes, did not reveal any significant correlation with these haplotypes, indicating that the haplotypes in the FLAP gene represent an independent genetic susceptibility factor for MI.

Table 7: The selected SNP haplotypes and the corresponding p-values

	p-val	RR	#aff	aff.frq.	carr.frq.	#con	con.frq.	PAR	SG13S99	SG13S25	SG13S377	SG13S106	SG13S114	SG13S89	SG13S30	SG13S32	SG13S42	SG13S35
B4	4.80E-05	2.08	903	0.106	0.2	619	0.054	0.11		G		G			G		A	
B5	2.40E-05	2.2	910	0.101	0.19	623	0.049	0.11	T	G		G			G		A	
B6	1.80E-06	2.22	913	0.131	0.24	623	0.063	0.14	T	G	G	G				A		G
A4	5.10E-06	1.81	919	0.159	0.29	623	0.095	0.14		G			T	G		A		
A5	2.60E-06	1.91	920	0.15	0.28	624	0.085	0.14	T	G			T	G		A		

Relative risk (RR), number of patients (#aff), allelic frequency in patients (aff.frq.), carrier frequency in patients (carr.frq.), number of controls (#con), allelic frequency in controls (con.frq.), population attributable risk (PAR). The patients used for this analysis were all unrelated within 4 meioses.

Haplotype association to female MI

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Before we had typed all the SNPs that eventually lead to the identification of A4 haplotype we performed a haplotype association analysis that included 437 female MI patients, 1049 male MI patients, and 811 controls that had been genotyped with several SNPs and 3 microsatellite markers. These markers were all located within 300 kb region encompassing the FLAP gene. In a case-control study of the MI patients using these data, several haplotypes were found, that were significantly over-represented in the female MI patients compared to controls (see Table 8). All these haplotypes were highly correlated with each other.

20 Table 8: haplotypes in the FLAP region (FLAP and flanking nucleotide sequences) that were associated with female MI.

SG13S421	SG13S418	SG13S419	SG13S420	DG13S166	SG13S106	SG13S114	SG13S121	SG13S122	SG13S88	SG13S181	SG13S184	D13S1238	DG13S2605	p-val	N _{aff}	aff.frq	N _{ctrl}	ctrl.frq	rel_risk	PAR	Info
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	C		T	0						G	-2		1.30E-05	455	0.108	811	0.048	2.4	0.122	0.615
	C		T	0		T		A	T		-2	0	7.61E-06	455	0.065	812	0.02	3.45	0.091	0.615
	C		T	0		T			T		-2	0	8.82E-06	455	0.065	812	0.02	3.47	0.092	0.602
	C		T	0		T	G		T		-2	0	9.31E-06	455	0.065	812	0.02	3.39	0.089	0.611
	C		T	0		T			T	G	-2	0	6.91E-06	455	0.063	812	0.019	3.54	0.09	0.624
	C	A	T	0		T			T		-2	0	9.76E-06	455	0.063	812	0.019	3.51	0.089	0.606
	C		T	0		T		A	T	G	-2		1.09E-05	455	0.063	811	0.019	3.41	0.086	0.618
	C		T	0		T			T	G	-2	0	1.10E-05	455	0.063	812	0.019	3.44	0.087	0.611
	C		T	0			G		T	G	-2	0	1.11E-05	455	0.063	812	0.018	3.56	0.086	0.589
	C		T	0			G		T	G	-2		1.22E-05	455	0.063	811	0.018	3.6	0.087	0.577
	C		T	0	G				T	G	-2	0	1.26E-05	455	0.063	812	0.02	3.35	0.088	0.629
	C		T	0				A	T	G	-2	0	8.59E-06	455	0.062	812	0.018	3.53	0.085	0.62
	C		T	0				A	T	G	-2		1.20E-05	455	0.062	811	0.019	3.42	0.086	0.617
	C		T	0			G	A	T	G	-2		1.21E-05	455	0.062	811	0.019	3.43	0.086	0.619
A	C		T	0			G		T	G	-2		7.93E-06	455	0.061	811	0.016	3.95	0.088	0.562
A	C		T	0					T	G	-2		1.09E-05	455	0.061	811	0.017	3.85	0.09	0.56
A	C		T	0		T			T	G	-2		5.00E-06	455	0.06	811	0.015	4.11	0.087	0.576
	C	A	T	0			G		T	G	-2		1.31E-05	455	0.06	811	0.017	3.66	0.085	0.586
A	C		T	0				A	T	G	-2		8.53E-06	455	0.059	811	0.016	3.85	0.085	0.593
A	C	A	T	0					T	G	-2		9.63E-06	455	0.058	811	0.015	4.03	0.085	0.565

Table 9 shows two haplotypes that are representative of these female MI risk haplotypes. The relative risk of these haplotypes were 2.4 and 4, and they were carried by 23% and 13% of female MI patients, respectively.

Table 9: Two representative variants of the female MI “at risk” haplotypes

	SG13S418	SG13S420	DG13S166	SG13S114	SG13S88	SG13S184	D13S1238	p-val	N _{aff}	aff.frq	N _{ctrl}	ctrl.frq	rel_risk	PAR	info
Female MI															
	C	T	0	T	T	G	-2	6.38E-06	4549	0.05	8095	0.01	4.0	0.08	0.57
	C	T	0			G	-2	2.74E-05	4476	0.10	8098	0.04	2.3	0.11	0.62

P-val: p-value for the association. **N_{aff}:** Number of patients used in the analysis. **Aff.frq:** haplotype frequency in patients. **N_{ctrl}:** number of controls used in the analysis. **Ctrl.frq:** Haplotype frequency in controls. **Rel_risk:** Relative risk of the haplotype. **PAR:** population attributable risk. **Info:** information content.

Table 10 shows that these same haplotypes were also over-represented in male MI patients compared to controls, although with lower relative risk. It should be noted that after typing and analysing more SNPs in the FLAP region these female MI “at risk” haplotypes could no longer be considered significant after adjusting for multiple testing.

Table 10: The frequencies of the female MI “at risk” haplotypes in male patients vs controls.

	SG13S418	SG13S420	DG13S166	SG13S114	SG13S88	SG13S184	D13S1238	p-val	N _{aff}	aff.frq	N _{ctrl}	ctrl.frq	rel_risk	PAR	Info
Male MI															
	C	T	0	T	T	G	-2	3.37E-01	1087	0.027	809	0.021	1.32	0.013	0.577
	C	T	0			G	-2	5.39E-01	1087	0.056	809	0.05	1.13	0.013	0.568

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P-val: p-value for the association. **N_{aff}:** Number of patients used in the analysis. **Aff.frq:** haplotype frequency in patients. **N_{ctrl}:** number of controls used in the analysis. **Ctrl.frq:** Haplotype frequency in controls. **Rel_risk:** Relative risk of the haplotype. **PAR:** population attributable risk. **Info:** information content.

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Table 11: The marker map for chromosome 13 used in the linkage analysis.

Location (cM)	Marker	Location (cM)	Marker
6	D13S175	63.9	D13S170
9.8	D13S1243	68.7	D13S265
13.5	D13S1304	73	D13S167
17.2	D13S217	76.3	D13S1241
21.5	D13S289	79.5	D13S1298
25.1	D13S171	81.6	D13S1267
28.9	D13S219	84.7	D13S1256
32.9	D13S218	85.1	D13S158
38.3	D13S263	87	D13S274
42.8	D13S326	93.5	D13S173

45.6	D13S153	96.7	D13S778
49.4	D13S1320	102.7	D13S1315
52.6	D13S1296	110.6	D13S285
55.9	D13S156	115	D13S293
59.8	D13S1306		

Table 12 Marker Map for the second step of Linkage Analysis

Location (cM)	Marker	Location (cM)	Marker
1.758	D13S175	42.585	D13S1248
9.235	D13S787	44.288	D13S1233
11.565	D13S1243	44.377	D13S263
16.898	D13S221	45.535	D13S325
17.454	D13S1304	45.536	D13S1270
18.011	D13S1254	45.537	D13S1276
18.59	D13S625	49.149	D13S326
19.308	D13S1244	49.532	D13S1272
19.768	D13S243	52.421	D13S168
22.234	D13S1250	52.674	D13S287
22.642	D13S1242	60.536	D13S1320
22.879	D13S217	64.272	D13S1296
25.013	D13S1299	71.287	D13S156
28.136	D13S289	76.828	D13S1306
28.678	D13S290	77.86	D13S170
29.134	D13S1287	82.828	D13S265
30.073	D13S260	91.199	D13S1241
31.98	D13S171	93.863	D13S1298
32.859	D13S267	97.735	D13S779
33.069	D13S1293	100.547	D13S1256
33.07	D13S620	102.277	D13S274
34.131	D13S220	111.885	D13S173
36.427	D13S219	112.198	D13S796
39.458	D13S1808	115.619	D13S778
40.441	D13S218	119.036	D13S1315
41.113	D13S1288	126.898	D13S285
41.996	D13S1253	131.962	D13S293

Table 13 shows the exons with positions that encode the FLAP protein, markers, polymorphisms and SNPs identified within the genomic sequence by the methods described herein.

NCBI build34; start chr. (bp)	NCBI build34; on stop chr. 13 (bp)	SNP/marker/ exon name	alias1	alias2	public SNP	Variation
28932432	28932432	SG13S421		DG00AAFQR	rs1556428	A/G
28960356	28960356	SG13S417		SNP13B_R1028729	rs1028729	C/T
28965803	28965803	SG13S418		SNP13B_Y1323898	rs1323898	A/G
28974627	28974627	SG13S44				A/G
28975101	28975101	SG13S45				C/G
28975315	28975315	SG13S46				A/G
28975353	28975353	SG13S50				C/T
28975774	28975774	SG13S52				A/G
28985244	28985244	SG13S53			rs1408167	A/C
28985303	28985303	SG13S55			rs1408169	A/G
28985423	28985423	SG13S56				G/T
28985734	28985734	SG13S57			rs6490471	C/T
28985902	28985902	SG13S58			rs6490472	A/G
29003869	29003869	SG13S59				C/G
29004696	29004696	SG13S60				A/G
29007670	29007670	SG13S419		SNP13B_K912392	rs912392	C/T
29015410	29015410	SG13S61				C/T
29025792	29025792	SG13S62				C/T
29026202	29026202	SG13S63			rs7997114	A/G
29026668	29026668	SG13S64				A/G
29038707	29038707	SG13S65				A/G
29042180	29042180	SG13S420		DG00AAFIV	rs2248564	A/T
29049355	29049355	SG13S66				A/G
29049446	29049446	SG13S67				C/T
29050416	29050416	SG13S69				A/C
29059348	29059348	SG13S70				A/G
29059383	29059383	SG13S71				A/G
29059402	29059402	SG13S72				G/T
29063702	29063949	D13S289				
29064359	29064753	DG13S166				
29066272	29066272	SG13S73				A/G
29070551	29070551	SG13S99	SNP_13_Y1323892	DG00AAFIU	rs1323892	C/T
29081983	29081983	SG13S382	FLA267479			A/G
29082200	29082200	SG13S383	FLA267696			A/G
29082357	29082357	SG13S384	FLA267853			A/G
29083350	29083350	SG13S381	FLA268846	DG00AAJER		C/G
29083518	29083518	SG13S366	FLA269014	DG00AAJES	rs4312166	A/G
29085102	29085102	SG13S385	FLA270742			C/T
29085190	29085190	SG13S386	FLA270830			A/G
29086224	29086224	SG13S1	FLA271864			G/T
29087473	29087473	SG13S2	FLA273371			A/G
29088090	29088090	SG13S367	FLA273988	DG00AAJEU	rs4474551	A/G
29088186	29088186	SG13S388	FLA274084			A/G
29088473	29088473	SG13S10	FLA274371			A/T

29089044	29089044	SG13S3	FLA274942			C/T
29089886	29089886	SG13S368	FLA275784	DG00AAJEV		C/T
29090025	29090025	SG13S369	FLA275923	DG00AAJEW		G/T
29090054	29090054	SG13S370	FLA275952	DG00AAJEX		A/G
29090997	29090997	SG13S4	FLA276895			G/C
29091307	29091307	SG13S5	FLA277205		rs4238133	G/T
29091580	29091580	SG13S389	FLA277478			A/G
29091780	29091780	SG13S90	FLA277678			A/C
29092287	29092287	SG13S390	FLA278185		rs5004913	A/G
29092536	29092536	SG13S6	FLA278434			A/G
29092594	29092594	SG13S391	FLA278492			A/G
29092947	29092947	SG13S392	FLA278845			G/T
29093964	29093964	SG13S371	FLA279888	DG00AAJEY	rs4409939	A/G
29094259	29094259	SG13S372	FLA280183	DG00AAJEZ		A/G
29094999	29094999	SG13S393	FLA280923			A/T
29096688	29096688	SG13S373	FLA282612	DG00AAJFA		A/G
29096813	29096813	SG13S374	FLA282737	DG00AAJFB		A/G
29096874	29096874	SG13S375	FLA282798	DG00AAJFC		C/T
29096962	29096962	SG13S376	FLA282886	DG00AAJFD		A/G
29097476	29097476	SG13S394	FLA283400			C/G
29097553	29097553	SG13S25	FLA283477			A/G
29098486	29098486	SG13S395	FLA284410			A/G
29098891	29098891	SG13S396	FLA284815			A/C
29098979	29098979	SG13S397	FLA284903			C/T
29101965	29101965	SG13S377	FLA287889	DG00AAJFF		A/G
29103909	29103909	SG13S189	FLA289833			C/G
29104271	29104271	SG13S100	FLA290195	DG00AAHIK	rs4073259	A/G
29104629	29104629	SG13S398	FLA290553			C/G
29104646	29104646	SG13S94	FLA290570		rs4073261	C/T
29105099	29105099	SG13S101	FLA291023		rs4075474	C/T
29106329	29106329	SG13S95	FLA292253			G/T
29106652	29106652	SG13S102	FLA292576			A/T
29107138	29107138	SG13S103	FLA293062			C/T
29107404	29107404	SG13S104	FLA293328			A/G
29107668	29107812	EXON1				
29107830	29107830	SG13S191	FLA293754	DG00AAFJT	rs4769055	A/C
29108398	29108398	SG13S105	FLA294322			A/G
29108579	29108579	SG13S106	FLA294503	DG00AAHII		A/G
29108919	29108919	SG13S107	FLA294843		rs4075131	A/G
29108972	29108972	SG13S108	FLA294896		rs4075132	C/T
29109112	29109112	SG13S109	FLA295036			A/G
29109182	29109182	SG13S110	FLA295106			A/G
29109344	29109344	SG13S111	FLA295268		rs4597169	C/T
29109557	29109557	SG13S112	FLA295481			C/T
29109773	29109773	SG13S113	FLA295697		rs4293222	C/G
29110096	29110096	SG13S114	FLA296020	DG00AAHID		A/T
29110178	29110178	SG13S115	FLA296102			A/T
29110508	29110508	SG13S116	FLA296432		rs4769871	C/T
29110630	29110630	SG13S117	FLA296554		rs4769872	A/G
29110689	29110689	SG13S118	FLA296613		rs4769873	C/T
29110862	29110862	SG13S119	FLA296786			A/G
29111889	29111889	SG13S120	FLA297813			C/T
29112174	29112174	SG13S121	FLA298098	DG00AAHIJ	rs4503649	A/G
29112264	29112264	SG13S122	FLA298188	DG00AAHIH		A/G
29112306	29112306	SG13S123	FLA298230			C/T
29112455	29112455	SG13S43	FLA298379		rs3885907	A/C

29112583	29112583	SG13S399	FLA298507		A/C
29112680	29112680	SG13S124	FLA298604	rs3922435	C/T
29113139	29113139	SG13S125	FLA299063		A/G
29114056	29114056	SG13S400	FLA299980		A/G
29114738	29114738	SG13S126	FLA300662		A/G
29114940	29114940	SG13S127	FLA300864		A/G
29115878	29115878	SG13S128	FLA302094	rs4254165	A/G
29116020	29116020	SG13S129	FLA302236	rs4360791	A/G
29116068	29116068	SG13S130	FLA302284		G/T
29116196	29116296	EXON2			
29116249	29116249	SG13S190	FLA302465		C/T
29116308	29116308	SG13S192	FLA302524	B_SNP_302524	rs3803277 A/C
29116344	29116344	SG13S193	FLA302560		A/G
29116401	29116401	SG13S88	FLA302617	B_SNP_302617	rs3803278 C/T
29116688	29116688	SG13S131	FLA302904		C/T
29117133	29117133	SG13S132	FLA303349		A/C
29117546	29117546	SG13S133	FLA303762	rs4356336	C/T
29117553	29117553	SG13S38	FLA303769	rs4584668	A/T
29117580	29117580	SG13S134	FLA303796		C/T
29117741	29117741	SG13S135	FLA303957	rs4238137	C/T
29117954	29117954	SG13S136	FLA304170	rs4147063	C/T
29118118	29118118	SG13S137	FLA304334	DG00AAHIG	rs4147064 C/T
29118815	29118815	SG13S86	FLA305031		A/G
29118873	29118873	SG13S87	FLA305089	DG00AAHOJ	A/G
29119069	29119069	SG13S138	FLA305285		C/T
29119138	29119138	SG13S139	FLA305354		C/G
29119289	29119289	SG13S140	FLA305505		A/G/T
29119462	29119462	SG13S141	FLA305678		C/T
29119740	29119740	SG13S39	FLA305956		G/T
29120939	29120939	SG13S142	FLA307155	rs4387455	C/T
29120949	29120949	SG13S143	FLA307165	rs4254166	C/T
29121342	29121342	SG13S144	FLA307558	rs4075692	A/G
29121572	29121572	SG13S145	FLA307788		C/G
29121988	29121988	SG13S146	FLA308204		C/T
29122253	29122253	SG13S26	FLA308469		C/T
29122283	29122283	SG13S27	FLA308499		A/G
29122294	29122294	SG13S147	FLA308510		C/T
29122298	29122298	SG13S28	FLA308514		G/T
29122311	29122311	SG13S148	FLA308527		G/T
29123370	29123370	SG13S98	FLA309586		G/T
29123635	29123635	SG13S149	FLA309851		A/G
29123643	29123643	SG13S29	FLA309859		A/C
29124188	29124259	EXON3			
29124441	29124441	SG13S89	FLA310657	B_SNP_310657	rs4769874 A/G
29124906	29124906	SG13S96	FLA311122		rs4072653 A/G
29125032	29125032	SG13S150	FLA311248		C/G
29125521	29125521	SG13S401	FLA311737		C/T
29125822	29125822	SG13S151	FLA312038		C/T
29125840	29125840	SG13S30	FLA312056		G/T
29127301	29127301	SG13S31	FLA313550		C/T
29128080	29128162	EXON4			
29128284	29128284	SG13S152	FLA314500		C/G
29128316	29128316	SG13S402	FLA314532	rs4468448	C/T
29128798	29128798	SG13S403	FLA315014	rs4399410	A/G
29129016	29129016	SG13S153	FLA315232		A/T
29129139	29129139	SG13S97	FLA315355		A/G
29129154	29129154	SG13S154	FLA315370		C/T

29129395	29129395	SG13S40	FLA315611		G/T
29129915	29129915	SG13S155	FLA316131		rs4769875 A/G
29130192	29130192	SG13S156	FLA316408		A/C
29130256	29130256	SG13S157	FLA316472		A/G
29130299	29130299	SG13S158	FLA316515		A/C
29130353	29130353	SG13S159	FLA316569		G/T
29130391	29130391	SG13S160	FLA316607		C/T
29130547	29130547	SG13S32	FLA316763		A/C
29131280	29131280	SG13S161	FLA317496		A/G
29131403	29131403	SG13S162	FLA317619		A/G
29131404	29131404	SG13S163	FLA317620		C/T
29131431	29131431	SG13S164	FLA317647		rs4769058 C/T
29131517	29131517	SG13S165	FLA317733		A/T
29131528	29131528	SG13S166	FLA317744		rs4769059 C/T
29131599	29131599	SG13S167	FLA317815		rs4769876 A/G
29132003	29132003	SG13S168	FLA318219		A/C
29133753	29133753	SG13S33	FLA319969		G/T
29134045	29134045	SG13S41	FLA320261		A/G
29134177	29134177	SG13S169	FLA320393		A/G
29134379	29134379	SG13S404	FLA320595		rs4427651 G/T
29135558	29135558	SG13S170	FLA321774		rs3935645 C/T
29135640	29135640	SG13S171	FLA321856		rs3935644 A/G
29135750	29135750	SG13S172	FLA321966		A/G
29135809	29135809	SG13S173	FLA322025		A/T
29135877	29135877	SG13S42	FLA322093		rs4769060 A/G
29136080	29136556	EXON5			
29136290	29136290	SG13S194	FLA322506		C/T
29136462	29136462	SG13S195	FLA322678		rs1132340 A/G
29136797	29136797	SG13S174	FLA323013		A/G
29137100	29137100	SG13S34	FLA323316		G/T
29137150	29137150	SG13S175	FLA323366		A/G
29137607	29137607	SG13S176	FLA323823		A/G
29137651	29137651	SG13S177	FLA323867		C/T
29137905	29137905	SG13S178	FLA324121		C/G
29138117	29138117	SG13S35	FLA324333		A/G
29138375	29138375	SG13S179	FLA324591		A/G
29138385	29138385	SG13S180	FLA324601		C/T
29138633	29138633	SG13S181	FLA324849	DG00AAHIF	rs4420371 C/G
29139153	29139153	SG13S182	FLA325369		C/T
29139277	29139277	SG13S183	FLA325493		rs4466940 C/T
29139435	29139435	SG13S184	FLA325651	DG00AAHOI	rs4445746 A/G
29139971	29139971	SG13S185	FLA326187		A/G
29140441	29140441	SG13S405	FLA326657		A/G
29140649	29140649	SG13S91	FLA326865		A/G
29140695	29140695	SG13S186	FLA326911		rs4769877 A/T
29140703	29140703	SG13S187	FLA326919		A/G
29140805	29140805	SG13S188	FLA327021	DG00AAJFE	A/G
29141049	29141049	SG13S406	FLA327265		C/T
29142392	29142392	SG13S92	FLA328644		rs4429158 C/T
29142397	29142397	SG13S93	FLA328649		A/G
29142712	29142712	SG13S36	FLA328964		C/T
29144013	29144013	SG13S407	FLA330265		C/T
29144203	29144203	SG13S408	FLA330455		C/T
29144234	29144589	D13S1238			
29144255	29144255	SG13S7	FLA330507		C/T
29144877	29144877	SG13S37	FLA331129		A/G

29144982	29144982	SG13S409	FLA331234
29144983	29144983	SG13S8	FLA331235
29145122	29145122	SG13S410	FLA331374
29145143	29145143	SG13S411	FLA331395
29145171	29145171	SG13S9	FLA331423
29145221	29145221	SG13S412	FLA331473
29145265	29145265	SG13S413	FLA331517

A/G
rs4491352 A/C
rs4319601 C/T
A/G
C/T
rs4769062 A/G
rs4238138 C/T

minor allele	minor allele frequenc y (%)	start position SEQ NO:1	end in position ID SEQ NO:1
G	10.32	432	432
G	30.46	28356	28356
T	37.38	33803	33803
G	0.545	42627	42627
G	1.111	43101	43101
G	0.328	43315	43315
C	0.495	43353	43353
A	6.993	43774	43774
C	30.876	53244	53244
G	6.731	53303	53303
T	0.353	53423	53423
C	31.356	53734	53734
A	30.935	53902	53902
G	5.492	71869	71869
A	1.812	72696	72696
G	35.00	75670	75670
C	1.314	83410	83410
T	3.521	93792	93792
A	30.031	94202	94202
A	1.724	94668	94668
A	0.369	106707	106707
A	13.66	110180	110180
A	20.779	117355	117355
T	5.965	117446	117446
A	16.923	118416	118416
A	34.364	127348	127348
A	8.537	127383	127383
T	25.536	127402	127402
		131702	131949
		132359	132753
A	37.302	134272	134272
C	6.25	138551	138551
A	0.49	149983	149983
A	14.08	150200	150200
G	0.62	150357	150357
G	14.01	151350	151350
T	0.58	151518	151518
C	30.21	153102	153102
A	10.95	153190	153190
G	30.00	154224	154224
A	27.95	155473	155473

G	2.41	156090	156090
A	0.39	156186	156186
T	10.23	156473	156473
T	15.17	157044	157044
T	13.60	157886	157886
G	12.44	158025	158025
A	13.45	158054	158054
G	14.59	158997	158997
T	26.84	159307	159307
A	12.73	159580	159580
C	43.67	159780	159780
A	12.18	160287	160287
A	8.38	160536	160536
G	0.62	160594	160594
T	12.34	160947	160947
G	25.34	161964	161964
C	0.24	162259	162259
T	25.66	162999	162999
A	14.84	164688	164688
G	12.37	164813	164813
C	14.55	164874	164874
G	11.99	164962	164962
C	14.66	165476	165476
A	12.21	165553	165553
A	0.79	166486	166486
C	10.15	166891	166891
C	3.53	166979	166979
A	12.45	169965	169965
C	0.62	171909	171909
G	31.55	172271	172271
G	4.94	172629	172629
C	15.51	172646	172646
T	27.91	173099	173099
G	14.74	174329	174329
T	1.17	174652	174652
T	1.28	175138	175138
A	2.17	175404	175404
		175668	175812
A	30.11	175830	175830
G	0.66	176398	176398
A	28.31	176579	176579
G	14.85	176919	176919
C	1.21	176972	176972
A	1.04	177112	177112
G	0.88	177182	177182
C	1.14	177344	177344
T	7.10	177557	177557
C	22.52	177773	177773
A	20.86	178096	178096
T	13.83	178178	178178
T	4.05	178508	178508
A	4.07	178630	178630
T	4.07	178689	178689
A	1.06	178862	178862

C	16.00	179889	179889
G	49.36	180174	180174
A	29.75	180264	180264
T	5.06	180306	180306
C	46.23	180455	180455
C	1.59	180583	180583
T	1.45	180680	180680
G	11.32	181139	181139
A	3.25	182056	182056
A	34.12	182738	182738
G	29.63	182940	182940
A	45.68	183878	183878
G	36.65	184020	184020
G	8.07	184068	184068
		184196	184296
T	1.02	184249	184249
A	49.57	184308	184308
A	0.58	184344	184344
C	24.71	184401	184401
T	7.19	184688	184688
A	1.10	185133	185133
T	37.65	185546	185546
A	45.50	185553	185553
T	1.22	185580	185580
T	0.89	185741	185741
T	36.69	185954	185954
T	29.11	186118	186118
A	30.19	186815	186815
G	3.29	186873	186873
T	36.96	187069	187069
G	36.63	187138	187138
T	37.34	187289	187289
C	1.15	187462	187462
T	9.91	187740	187740
C	3.36	188939	188939
T	36.24	188949	188949
A	31.58	189342	189342
G	0.45	189572	189572
T	1.14	189988	189988
T	46.57	190253	190253
A	10.34	190283	190283
T	8.00	190294	190294
T	33.71	190298	190298
T	2.29	190311	190311
G	1.19	191370	191370
A	1.01	191635	191635
A	47.88	191643	191643
		192188	192259
A	4.68	192441	192441
G	29.72	192906	192906
C	8.22	193032	193032
C	21.10	193521	193521
T	8.57	193822	193822
T	23.23	193840	193840
T	24.20	195301	195301
		196080	196162

C	23.89	196284	196284
T	19.33	196316	196316
G	11.50	196798	196798
T	3.08	197016	197016
A	9.72	197139	197139
T	0.98	197154	197154
T	2.24	197395	197395
A	1.43	197915	197915
A	1.80	198192	198192
G	2.38	198256	198256
A	0.61	198299	198299
G	2.55	198353	198353
T	0.83	198391	198391
C	48.50	198547	198547
G	2.44	199280	199280
G	2.45	199403	199403
C	2.45	199404	199404
C	2.55	199431	199431
T	20.00	199517	199517
T	2.46	199528	199528
A	3.50	199599	199599
C	8.39	200003	200003
T	8.99	201753	201753
G	5.41	202045	202045
G	4.12	202177	202177
G	38.33	202379	202379
C	32.77	203558	203558
G	48.03	203640	203640
G	1.67	203750	203750
A	0.68	203809	203809
G	42.44	203877	203877
		204080	204556
T	0.30	204290	204290
G	2.46	204462	204462
G	0.56	204797	204797
G	30.23	205100	205100
A	2.40	205150	205150
A	2.24	205607	205607
T	1.64	205651	205651
C	1.40	205905	205905
A	9.52	206117	206117
A	48.14	206375	206375
T	2.50	206385	206385
C	49.41	206633	206633
T	2.36	207153	207153
T	12.07	207277	207277
A	16.67	207435	207435
G	7.66	207971	207971
A	9.66	208441	208441
A	7.78	208649	208649
A	25.71	208695	208695
A	1.43	208703	208703
G	4.71	208805	208805
T	0.56	209049	209049
T	8.33	210392	210392

A	7.23	210397	210397
C	15.88	210712	210712
T	3.29	212013	212013
T	0.30	212203	212203
		212234	212589
T	16.28	212255	212255
G	16.70	212877	212877
A	1.93	212982	212982
C	30.64	212983	212983
T	20.57	213122	213122
A	1.54	213143	213143
C	16.37	213171	213171
A	7.42	213221	213221
T	1.91	213265	213265

Table 14: Extended 4 microsatellite marker haplotypes

4 markers :	pos.rr-frqgt1perc												Markers
Length	p-val	RR	N_af	P_al	P_ca	N_ct	P_al	P_ca	Alleles				
0.88	4.71E-06	6.23	428	0.065	0.125	721	0.011	0.022	0	-12	-6	0	DG13S80 DG13S83 DG13S1110 DG13S163
0.82	8.60E-06	INF	438	0.032	0.062	720	0	0	0	4	2	14	DG13S111 1 DG13S1103 D13S1287 DG13S1061
0.67	6.98E-06	19.91	435	0.03	0.059	721	0.002	0.003	8	6	0	8	DG13S1103 DG13S163 D13S290 DG13S1061
0.767	4.85E-06	26.72	436	0.048	0.094	721	0.002	0.004	0	0	2	12	DG13S1101 DG13S166 D13S1287 DG13S1061
0.515	1.93E-06	INF	422	0.048	0.094	721	0	0	2	0	0	6	DG13S166 DG13S163 D13S290 DG13S1061
0.864	1.68E-06	INF	424	0.024	0.048	717	0	0	0	2	0	-16	DG13S166 DG13S163 DG13S1061 DG13S293
0.927	5.38E-06	INF	435	0.034	0.067	720	0	0	4	2	14	3	DG13S1103 D13S1287 DG13S1061 DG13S301

Alleles #'s: For SNP alleles A = 0, C = 1, G = 2, T = 3; for microsatellite

alleles: the CEPH sample (Centre d'Etudes du Polymorphisme Humain, genomics repository) is used as a reference, as described above.

Length=length of haplotype in Mb. P-val=p-value. RR=Relative risk. N af=Number of patients. P al=allelic frequency of haplotype. P ca =carrier frequency of haplotype. N ct= number of controls. Alleles= alleles in the haplotype. Markers= markers in the haplotype.

Table 15: Extended 5 microsatellite marker haplotypes

5markers		pos.rr-frqgt1perc															
Length	p-val	RR	N_af	P_al	P_ca	N_ct	P_al	P_ca	Alleles								Markers
0.851	7.45E-06	15.43	413	0.034	0.067	715	0.002	0.005	0	18	0	0	0	0	0	0	DG13S79 D13S1299 DG13S87 D13S1246 DG13S166
0.964	8.07E-06	INF	437	0.023	0.045	721	0	0	0	-12	6	8	6	6	6	6	DG13S79 DG13S83 DG13S1104 DG13S1103 DG13S163
0.964	2.38E-06	INF	437	0.026	0.052	720	0	0	0	6	0	8	6	6	6	6	DG13S79 DG13S1104 DG13S172 DG13S1103 DG13S163
0.931	7.05E-06	5.8	429	0.068	0.131	721	0.012	0.025	0	-6	0	0	-2	0	0	0	DG13S79 DG13S1110 DG13S175 DG13S166 D13S1238
0.964	8.13E-06	INF	434	0.021	0.041	721	0	0	0	3	8	2	6	6	6	6	DG13S79 DG13S1098 DG13S1103 DG13S166 DG13S163
0.597	9.78E-06	4.58	428	0.074	0.143	717	0.017	0.034	-6	0	0	0	-2	0	0	0	DG13S1110 DG13S89 DG13S175 DG13S166 D13S1238
0.896	6.92E-06	INF	428	0.026	0.051	721	0	0	-12	-6	0	-2	2	2	2	2	DG13S83 DG13S1110 DG13S166 D13S1238 D13S290
0.722	2.18E-06	INF	453	0.026	0.051	738	0	0	-6	0	0	-2	2	2	2	2	DG13S1110 D13S289 DG13S166 D13S1238 D13S290
0.982	7.88E-06	INF	437	0.028	0.055	721	0	0	0	0	4	2	14	14	14	14	DG13S87 DG13S175 DG13S1103 D13S1287 DG13S1061
0.841	8.88E-06	INF	438	0.032	0.062	720	0	0	0	0	4	2	14	14	14	14	DG13S89 DG13S1111 DG13S1103 D13S1287 DG13S1061
0.841	9.67E-07	INF	435	0.029	0.057	721	0	0	0	8	6	0	8	8	8	8	DG13S89 DG13S1103 DG13S163 D13S290 DG13S1061
0.982	7.90E-06	18.63	437	0.026	0.052	721	0.001	0.003	0	4	0	2	14	14	14	14	DG13S87 DG13S1103 DG13S166 D13S1287 DG13S1061
0.841	3.52E-06	28.52	436	0.048	0.094	721	0.002	0.004	0	0	0	2	12	12	12	12	DG13S89 DG13S1101 DG13S166

																D13S1287 DG13S1061
																DG13S175 DG13S1103 DG13S163 D13S290 DG13S1061
0.705	5.28E-06	INF	435	0.027	0.053	721	0	0	0	8	6	0	8			DG13S89 DG13S166 DG13S163 D13S290 DG13S1061
0.841	4.21E-06	INF	422	0.048	0.093	721	0	0	0	2	0	0	6			DG13S1101 DG13S175 DG13S166 D13S1287 DG13S1061
0.767	4.02E-06	28.11	436	0.049	0.095	721	0.002	0.004	0	0	0	2	12			DG13S1101 DG13S172 DG13S166 D13S1287 DG13S1061
0.767	1.29E-06	31.07	436	0.047	0.092	721	0.002	0.003	0	0	0	2	12			DG13S175 DG13S166 DG13S163 D13S290 DG13S1061
0.705	4.25E-07	INF	422	0.048	0.093	721	0	0	0	2	0	0	6			DG13S172 DG13S1103 DG13S166 D13S1287 DG13S1061
0.683	6.58E-06	INF	437	0.029	0.056	721	0	0	0	4	0	2	14			DG13S1101 DG13S166 D13S290 D13S1287 DG13S1061
0.767	2.85E-06	32.43	436	0.044	0.087	721	0.001	0.003	0	0	0	2	12			D13S289 DG13S166 DG13S163 D13S1287 DG13S293
0.865	9.58E-06	18.39	451	0.023	0.045	739	0.001	0.003	0	0	2	2	16			D13S289 DG13S166 DG13S163 DG13S1061 DG13S293
0.865	5.08E-06	INF	453	0.019	0.038	739	0	0	0	0	2	0	16			DG13S1103 DG13S166 D13S1287 DG13S1061
0.927	1.02E-07	27.65	437	0.037	0.073	721	0.001	0.003	4	0	2	14	3			DG13S301

Length=length of haplotype in Mb. P-val=p-value. RR=Relative risk. N af=Number of patients. P al=allelic frequency of haplotype. P ca =carrier frequency of haplotype. N ct= number of controls. Alleles= alleles in the haplotype. Markers= markers in the haplotype

EXAMPLE 2: RELATIONSHIP BETWEEN POLYMORPHISM IN THE 5-LIPOXYGENASE PROMOTER AND MI

5 A family of mutations in the G-C rich transcription factor binding region of the 5-LO gene has previously been identified. These mutations consist of deletion of one, deletion of two, or addition of one zinc finger (Sp1/Egr-1) binding sites in the region 176 to 147 bp upstream from the ATG translation start site where there are normally 5 Sp1 binding motifs in tandem. These naturally occurring mutations in the human 5-LO
10 gene promoter have been shown to modify transcription factor binding and reporter gene transcription. The capacity of the mutant forms of DNA to promote transcription of CAT reporter constructs have been shown to be significantly less than that of the wild type DNA (*J. Clin. Invest.* Volume 99, Number 5, March 1997, 1130-1137). To test whether 5-LO is associated with the atherosclerotic diseases, particularly myocardial
15 infarction (MI) in the human population, this promoter polymorphism, consisting of variable number of tandem Sp1/Egr-1 binding sites, was genotyped in 1112 MI patients, 748 patients with PAOD, and 541 stroke patients.

The results, shown in Table 16, demonstrate that the wild type allele (which represents the allele with the most active promoter and thus with the highest expression of the 5-
20 LO mRNA; *J. Clin. Invest.* Volume 99, Number 5, March 1997, 1130-1137) is significantly associated with MI (RR=1.2, $p<0.05$). The results are consistent with a disease hypothesis that increased expression of the 5-LO plays a role in the pathogenesis of MI.

Table 16

	N_aff	Frq_aff	N_ctrl	Frq_ctrl	Risk Ratio	P-value
MI patients	1112	0.8701	734	0.8501	1.1803	0.048
Independent	969	0.8720	734	0.8501	1.2013	0.037
Males	646	0.8740	734	0.8501	1.2232	0.039
Females	465	0.8645	734	0.8501	1.1249	0.180
Age of onset < 60	522	0.8745	734	0.8501	1.2286	0.046
Males	353	0.8768	734	0.8501	1.2542	0.053
Females	169	0.8698	734	0.8501	1.1779	0.202
PAOD patients	748	0.8763	734	0.8501	1.2492	0.022
Independent	703	0.8755	734	0.8501	1.2400	0.027
Males	473	0.8774	734	0.8501	1.2613	0.033
Females	275	0.8745	734	0.8501	1.2289	0.092
Stroke patients	541	0.8743	734	0.8501	1.2262	0.046
Males	326	0.8758	734	0.8501	1.2427	0.067
Females	215	0.8721	734	0.8501	1.2019	0.144
Cardio / Large V	202	0.8861	734	0.8501	1.3719	0.038
Cardioembolic	114	0.8772	734	0.8501	1.2592	0.165
Large Vessel	88	0.8977	734	0.8501	1.5474	0.053
Small Vessel	77	0.8831	734	0.8501	1.2791	0.163
Hemorrhagic	27	0.9259	734	0.8501	2.2035	0.081

single sided p-values: Fisher exact test. N_aff= number of affected individuals;

Frq_aff= frequency of the wild type allele of the promoter polymorphism in the

affected group; N_ctrl= number of controls; Frq_ctrl= frequency of the wild type allele

5 of the promoter polymorphism in the control group;

EXAMPLE 3: ELEVATED LTE4 BIOSYNTHESIS IN INDIVIDUALS WITH THE FLAP MI-RISK HAPLOTYPE

Based on the known function of the end products of the leukotriene pathway
 10 and based on our 5-LO association data, the association of the FLAP haplotype with
 MI is best explained by increased expression and/or increased function of the FLAP
 gene. In other words, those individuals that have a “at risk” FLAP haplotype have
 either, or both, increased amount of FLAP, or more active FLAP. This would lead to
 increased production of leukotrienes in these individuals.

To demonstrate this theory, LTE4, a downstream leukotriene metabolite, was measured in patient serum samples. A quantitative determination of LTE4 in human serum was performed by liquid chromatography coupled with tandem mass spectrometry. The protocol was performed as follows:

5

ANALYTICAL METHOD

Table P1 (Protocol 1): List of Abbreviations

CAN	Acetonitrile
IS	Internal standard
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LOQ	Limit of quantification
QCs	Quality controls
R ²	Coefficient of determination
SS	Spiking solution

10

Apparatus and conditions

Table P2: Analytical apparatus and conditions

Instruments / Conditions	Details			
Analytical column	Zorbax extend C ₁₈ , 3.5µm (50 x 2.1 mm)			
Column temperature	Ambient			
Pump and flow	Hewlett Packard Series 1100 Binary pump delivering 0.3 ml/min			
Mobile phase	A: Buffer: Acetonitrile:H ₂ O (5:95 % v/v). (Containing 10 mM Ammonium Acetate and 0.1% Acetic acid at pH 4.6). B: Buffer: Acetonitrile:H ₂ O (95:5 % v/v). (Containing 10 mM Ammonium Acetate and 0.1% Acetic acid at pH 4.6).			
Gradient	Time	%A	%B	Flow rate
	0.00	30	70	0.3 ml/min
	1.00	30	70	0.3 ml/min
	1.50	90	10	0.3 ml/min
	6.00	90	10	0.3 ml/min
	6.50	30	70	0.3 ml/min
	10.00	30	70	0.3 ml/min
Sample injection	HTC PAL autosampler 10 µl onto the HPLC column			
Mass Spectrometric system	Quattro Ultima™ Tandem MS/MS, Micromass. England.			
Recording and integration	Mass Lynx, version 3.5. All chromatograms and reports are printed out in hardcopy and stored in electronic form on the workstation hard disk drive. Recording time was 10 min.			
Retentions times	LTE ₄ ~ 3.05 min. LTE ₄ -d ₃ ~ 3.05 min.			
Ionization mode	Electrospray atmospheric pressure in negative ion mode			
Scan mode	Multiple reaction monitoring (MRM)			
	Compound	Parent ion	Daughter ion	

	LTE ₄	438.2	333.2
	LTE ₄ -d ₃	441.2	336.2

Other instruments

Table P3: The apparatus used for sample treatment and measurements

Apparatus	Brand	Type
Pipette	Eppendorf	Edos 5221
Pipette	Labsystems	Finnpipette 200 µl
Centrifuge	Eppendorf	5417C
Evaporation unit	Porvair	Ultravap
Vibrofix	Ika-Werk Thermolyne	VF-1 Maxi-mix III™, 65800
Balance	Sartorius	LA 120 S
Ultra sonic bath	Cole Parmer	8891

Materials

5 Table P4: Reagents for sample treatment and measurements

Reagent	Manufacturer	Quality	Art no.
Acetonitrile (ACN)	Rathburn	HPLC grade	RH 1016
Methanol	Rathburn	HPLC grade	RH 1019
Ammonium acetate	Merck	Pro analysis	1116

Table P5: Reference substances

	Details	Reference
Reference standards	Leukotrine E ₄ from Cayman Chemical, MI, USA	20410
Internal standards	Leukotriene E ₄ -20, 20,20-d ₃ from Biomol, PA, USA	S10120

Stock solutions

A stock solution of LTE₄ was prepared by the supplier at a concentration of 100µg/ml in methanol. The stock solution was diluted to a concentration of 20µg/ml in methanol and this working solution (WS-1) was kept refrigerated at 2-8°C.

- 5 An internal standard stock solution (LTE₄-d₃) was prepared by the supplier at concentration of 49.5µg/ml. The stock solution was diluted to a concentration of 1µg/ml in methanol and this working solution was kept refrigerated at 2-8°C.

Preparation of spiking solutions, calibration standards and quality control samples

- Spiking solutions (SS) in the concentration range of 1 ng/ml to 10000 ng/ml
10 were prepared by dilution of the working Solution.

The following spiking solutions were prepared:

Table P6: Spiking solutions for calibration standards

SS	Concentration (ng/ml)	Preparation
1	10000	500µl of WS-1 (20µg/ml) diluted to 1.0 ml with 70% MeOH/water
2	1000	100µl of SS-1 was diluted to 1.0 ml with 70% MeOH/water
3	100	100µl of SS-2 was diluted to 1.0 ml with 70% MeOH/water
4	30	300µl of SS-3 was diluted to 1.0 ml with 70% MeOH/water
5	20	200µl of SS-3 was diluted to 1.0 ml with 70% MeOH/water
6	16	160µl of SS-3 was diluted to 1.0 ml with 70% MeOH/water
7	12	120µl of SS-3 was diluted to 1.0 ml with 70% MeOH/water
8	8.0	400µl of SS-5 was diluted to 1.0 ml with 70% MeOH/water
9	4.0	200µl of SS-5 was diluted to 1.0 ml with 70% MeOH/water
10	2.0	100µl of SS-5 was diluted to 1.0 ml with 70% MeOH/water
11	1.4	175µl of SS-8 was diluted to 1.0 ml with 70% MeOH/water
12	1.0	125µl of SS-8 was diluted to 1.0 ml with 70% MeOH/water

Table P7: Spiking solutions for quality controls

SS	Concentration (ng/ml)	Preparation
13	14	140µl of SS-3 was diluted to 1.0 ml with 70% MeOH/water
14	6.0	300µl of SS-5 was diluted to 1.0 ml with 70% MeOH/water
15	2.4	120µl of SS-5 was diluted to 1.0 ml with 70% MeOH/water

After preparation, spiking solutions for calibration standards and quality controls were kept refrigerated at 2-8°C.

5

Preparation of calibration standards and quality controls

Fresh calibration standards and quality controls (QCs) were prepared each day by spiking blank plasma as described in Tables P8 and P9, respectively.

10 Table P8: Preparation of calibration standards

Concentration (ng/ml)	SS (µl)	Blank Plasma
1500	20 µl of the SS-4 (30ng/ml)	380 µl
1000	20 µl of the SS-5 (20ng/ml)	380 µl
800	20 µl of the SS-6 (16ng/ml)	380 µl
600	20 µl of the SS-7 (12ng/ml)	380 µl
400	20 µl of the SS-8 (8ng/ml)	380 µl
200	20 µl of the SS-9 (4.0ng/ml)	380 µl
100	20 µl of the SS-10 (2.0ng/ml)	380 µl
70	20µl of the SS-11 (1.4ng/ml)	380 µl
50	20µl of the SS-12 (1.0ng/ml)	380 µl

Table P9: Preparation of quality controls

Concentration (ng/ml)	SS (μl)	Blank Plasma
800	20 μl of the SS-13 (14ng/ml)	380 μl
40	20μl of the SS-14 (6.0ng/ml)	380 μl
8.0	20μl of the SS-15 (2.4ng/ml)	380 μl

5 *Sample preparation*

Aliquots of 400 μl of each study sample, calibration standards, QC samples and control blank are pipetted into an eppendorf vial. All samples apart from blank are then spiked with 20 μl of internal standard working solution and the samples are then vortex-mixed for few seconds. The pH of the plasma samples is adjusted to pH 4.5 using 60 μl of 10% acetic acid and centrifuged for 10 min. at 4100 rpm immediately before the extraction. The solid phase extraction 96-well plate is conditioned with 1 ml methanol and 1 ml water. Then 400μl of the plasma samples are loaded on the plate. Vacuum is applied, followed by drying the disk for 1 min. After being washed with 2ml water and 1 ml 30% methanol in 2% acetic acid. Next the plate is eluted with 0.6 ml methanol. The plate is then dried for few minutes. The methanol eluate is evaporated almost to dryness under a stream of nitrogen at 45°C. The residue is reconstituted in 30 μl mobile phase and vortex-mixed for few min. Subsequently, the solutions are centrifuged for 10 min at 10.000 rpm. and 10 μl are injected by the autosampler into the LC-MS/MS system for quantification.

20

PERFORMANCE OF MEASUREMENTS

The samples will be prepared and measured in batches and a typical batch will consist of:

One set of calibration standards, one extra lowest calibration standard and one blank.

25 Samples collected from a 16 individuals and one set of control samples (C_L , C_M , C_H)

Samples collected from a 17 individuals and one set of control samples (C_L , C_M , C_H)

QUANTITATIVE DETERMINATION OF ANALYTE IN PLASMA SAMPLES

The standard curve is calculated from the peak area ratios

5 ANALYTE/INTERNAL STANDARD of the calibration standards and their nominal ANALYTE concentrations. The unknown samples for LTE_4 were calculated from a quadratic regression equation where a weighted curve, $1/X^2$, is used. The measured peak area of the samples was converted into pictogram of ANALYTE per milliliter (pg/ml) of plasma according to the calculated equation for the standard curve.

10 The calculation of the regression for the standard curve and the calculations of the concentration of the unknown samples and the control samples are performed with MassLynx Software.

15 *ACCEPTANCE CRITERIA*

Calibration standards

The coefficient of determination (R^2) for the calibration curve must exceed 0.98.

The calibration curve included the concentration range from 50pg/ml –
20 1500pg/ml.

Concentration of the calibration standards must be within $\pm 25\%$ of their nominal value when recalculated from the regression equation. Calibration standards that fail these criteria (at most 3 in each run) are rejected and the calibration performed again with the remaining standards. If the standard curve is not accepted, the samples must be
25 reanalyzed.

Control samples

At least two thirds of the analysed quality controls must be within $\pm 25\%$ of their nominal value when calculated from regression equation. If more than a third of the controls fail, the samples must be reanalyzed.

RESULTS

Table 17 (below) shows that the female MI “at risk” haplotype was more associated with female MI patients who have high LTE4 levels (top 50th percentile), than with female MI patients who have low levels of LTE4 (bottom 50th percentile).

In addition, haplotype analysis, comparing female MI patients with high levels of LTE4 with female patients with low levels, showed that those with high levels had increased prevalence of the “at risk” haplotype by 1.6 fold (see Table 18). Although the association did not rise to the level of statistical significance, the results show clearly that the “at risk” haplotypes are enriched in the MI patient group that has high levels of LTE4. The carrier frequency of the “at risk” haplotypes are 12% and 20%, respectively, in the whole female MI group, but go up to 15% and 24%, respectively, in the female MI group that has high levels of LTE4. Correspondingly, the carrier frequency of the “at risk” haplotypes decrease to 8% and 18%, respectively, in the group of female MI that has low levels of LTE4 (Note carrier frequencies are twice the disease allele frequency times 1 minus the disease allele frequency plus the square of the disease allele frequency).

Note that LTE4 may simply reflect the leukotriene synthesis rate of the leukotriene synthetic pathway upstream of the key leukotriene metabolite involved in MI risk. For example, leukotriene B4 is probably more likely than leukotriene E4 to be involved in the inflammatory aspects of MI plaques but since B4 has a short half life, it is difficult to measure reliably in serum samples, while E4 has long term stability.

Table 17: Association of the at risk haplotypes for female MI, with female MI who
25 also have high levels of LTE4 (>50pg/ml (roughly the upper 50th percentile)).

[illegible]

	C	T	0	T	T	G	-2	4.65E-02	185	0.040	809	0.015	2.67	0.048	0.511
	C	T	0			G	-22	88E-02	182	0.087	809	0.048	1.89	0.08	0.622

P-val: p-value for the association. **N_{aff}:** Number of patients used in the analysis. **Aff.frq:** haplotype frequency in patients. **N_{ctrl}:** number of controls used in the analysis. **Ctrl.frq:** Haplotype frequency in controls. **Rel_{risk}:** Relative risk of the haplotype. **PAR:** population attributable risk. **Info:** information content. Less association was found between the at risk haplotype for female MI, with female MI who also have low levels of LTE4 (<50pg/ml).

10

Table 18: Association between haplotypes that were most significantly associated with female MI, and serum LTE4 levels.

	SG13S418	SG13S420	DG13S166	SG13S114	SG13S88	SG13S184	D13S1238	p-val	N _{aff}	aff.frq	N _{ctrl}	ctrl.frq	rel _{risk}	PAR	info
High vs low LTE4															
	C	T	0	T	T	G	-2	1.61E-01	221	0.084	185	0.054	1.61	0.063	0.689
	C	T	0			G	-2	1.20E-01	220	0.13	182	0.088	1.54	0.089	0.686

P-val: p-value for the association. **N_{aff}:** Number of patients used in the analysis. **Aff.frq:** haplotype frequency in patients. **N_{ctrl}:** number of controls used in the analysis. **Ctrl.frq:** Haplotype frequency in controls. **Rel_{risk}:** Relative risk of the haplotype. **PAR:** population attributable risk. **Info:** information content. Here, the group of affected individuals were defined as female MI patients with high serum LTE4 (higher than 50 pg/ml) and the control group is defined as female MI patients with low serum LTE4 (below 50 pg/ml).

EXAMPLE 4: ELEVATED LTE4 CORRELATED WITH ELEVATED C-REACTIVE PROTEIN (CRP)

The relationship between the increased production of leukotrienes and the inflammatory marker CRP, a well established risk factor for MI, was then explored.

As shown in FIG. 5, a significant positive correlation was found between serum LTE4 levels and serum CRP levels.

EXAMPLE 5: ASSESSMENT OF LEVEL OF CRP IN PATIENTS WITH AT-RISK HAPLOTYPE

The level of CRP in female patients with female MI at-risk haplotypes was assessed, in order to assess whether there was a presence of a raised level of inflammatory marker in the presence of the female MI at-risk haplotype. Results are shown in Table 19. Although the association did not rise to the level of statistical significance, it was demonstrated that the average CRP was elevated in those patients with the at-risk haplotype versus those without it.

10

Table 19:
All female patients

		no	Mean CRP	SE CRP
affecteds:	With haplotype.	155	4.91	8.7
	Not with haplotype.	218	4.35	6.13

EXAMPLE 6: ELEVATED SERUM LTE4 LEVELS IN MI PATIENTS VERSUS CONTROLS

The end products of the leukotriene pathway are potent inflammatory lipid mediators that can potentially contribute to development of atherosclerosis and destabilization of atherosclerotic plaques through lipid oxidation and/or proinflammatory effects. Examples one through five show that: 1) MI correlates with genetic variation at FLAP; 2) MI correlates with high expression promoter polymorphism at 5-LO; 3) C-reactive protein levels correlate with serum leukotriene E4; and 4) Patients with MI-risk FLAP haplotypes have higher levels of serum leukotriene E4 and CRP. Based on these data, it was hypothesized that serum leukotriene E4 levels correlate with MI risk.

To test this hypothesis, LTE4, a downstream leukotriene metabolite, was measured in 488 female MI patient and 164 control serum samples. The LTE4 levels for the patients were higher than that for the controls using a one-sided Wilcoxon rank-sum test. The p-value of the difference was 0.0092, thus confirming our hypothesis. Therefore, elevated leukotriene E4 represents a risk factor for MI. Serum or plasma

LTE4 levels may be used to profile the MI risk for individuals to aid in deciding which treatment and lifestyle management plan is best for primary or secondary MI prevention. In the same way other leukotriene metabolites may be used to risk profile for MI.

5

EXAMPLE 7: INCREASED LTB4 PRODUCTION IN ACTIVATED NEUTROPHILS FROM MI PATIENTS

A principal bioactive product of one of the two branches of the 5-LO pathway is

10 LTB4. To determine whether the patients with past history of MI have increased activity of the 5-LO pathway compared to controls, the LTB4 production in isolated blood neutrophils was measured before and after stimulation *in vitro* with the calcium ionophore, ionomycin. No difference was detected between the LTB4 production in resting neutrophils from MI patients or controls (results not shown). In contrast,

15 LTB4 generation by neutrophils from MI patients stimulated with the ionophore was significantly greater than by neutrophils from controls at 15 and 30 minutes, respectively (FIG. 7.1). Moreover, as shown in FIG. 7.2, the observed increase in the LTB4 release was largely accounted for by male carriers of haplotype A4, whose cells produced significantly more LTB4 than cells from controls (P value =0.0042) (Table

20 20). As shown in Table 20, there was also a heightened LTB4 response in males who do not carry HapA but of borderline significance. This could be explained by additional variants in the FLAP gene that have not been uncovered, or alternatively in other genes belonging to the 5-LO pathway, that may account for upregulation in the LTB4 response in some of the patients without the FLAP at-risk haplotype. As shown

25 in Table 20, differences in LTB4 response were not detected in females. However, due to a small sample size this cannot be considered conclusive. Taken together, the elevated levels of LTB4 production of stimulated neutrophils from male carriers of the at-risk haplotype suggest that the disease associated variants in the FLAP gene increase FLAP's response to factors that stimulate inflammatory cells, resulting in increased

30 leukotriene production and increased risk for MI.

Methods

Isolation and activation of peripheral blood neutrophils

50ml of blood were drawn into EDTA containing vacutainers from 43 MI patients and 35 age and sex matched controls. All blood was drawn at the same time in the
5 early morning after 12 hours of fasting. The neutrophils were isolated using Ficoll-Paque PLUS (Amersham Biosciences).

Briefly, the red cell pellets from the Ficoll gradient were harvested and red blood cells subsequently lysed in 0.165 M NH_4Cl for 10 minutes on ice. After washing with PBS, neutrophils were counted and plated at 2×10^6 cells/ml in 4ml cultures of 15%
10 Fetal calf serum (FCS) (GIBCO BRL) in RPMI-1640 (GIBCO BRL). The cells were then stimulated with maximum effective concentration of ionomycin ($1 \mu\text{M}$). At 0, 15, 30, 60 minutes post ionomycin addition 600 μl of culture medium was aspirated and stored at -80°C for the measurement of LTB_4 release as described below. The cells
15 were maintained at 37°C in a humidified atmosphere of 5% CO_2 /95% air. All samples were treated with indomethasine ($1 \mu\text{M}$) to block the cyclooxygenase enzyme.

Ionomycin-induced release of LTB_4 in neutrophils

LTB_4 Immunoassay (R&D systems) was used to quantitate LTB_4 concentration in supernatant from cultured ionomycin stimulated neutrophils. The assay used is
20 based on the competitive binding technique in which LTB_4 present in the testing samples (200 μl) competes with a fixed amount of alkaline phosphatase-labelled LTB_4 for sites on a rabbit polyclonal antibody. During the incubation, the polyclonal Ab becomes bound to a goat anti-rabbit Ab coated onto the microplates. Following a wash to remove excess conjugate and unbound sample, a substrate solution is added to the
25 wells to determine the bound enzyme activity. The color development is stopped and the absorbance is read at 405 nm. The intensity of the color is inversely proportional to the concentration of LTB_4 in the sample. Each LTB_4 measurement using the LTB_4 Immunoassay, was done in duplicate.

Table 20: LTB4 levels after ionomycin stimulation of isolated neutrophils^a

Phenotype (n)	After 15 Minutes		After 30 Minutes	
	Mean (SD)	P value	Mean (SD)	P value
Controls (35)	4.53 (1.00)		4.67 (0.88)	
Males (18)	4.61 (1.10)		4.68 (1.07)	
Females (17)	4.51 (0.88)		4.67 (0.62)	
MI (41)	5.18 (1.09)	0.011	5.24 (1.06)	0.016
Carriers(16)	5.26 (1.09)	0.027	5.27 (1.09)	0.051
Non-carriers (24)	5.12 (1.08)	0.040	5.22 (1.03)	0.035
MI males (28)	5.37 (1.10)	0.0033	5.38 (1.09)	0.0076
Carriers(10)	5.66 (1.04)	0.0042	5.58 (1.12)	0.013
Non-carriers (18)	5.20 (1.09)	0.039	5.26 (1.05)	0.041
MI females (13)	4.78 (0.95)	0.46	4.95 (0.92)	0.36
Carriers(6)	4.59 (0.80)	0.90	4.75 (0.82)	0.85
Non-carriers (7)	4.94 (1.04)	0.34	5.12 (0.96)	0.25

^aMean \pm SD of log-transformed values of LTB4 levels of ionomycin-stimulated neutrophils from MI patients and controls. Results are shown for two time points: 15 and 30 minutes. The results for males and females and for MI male and female carriers and non-carriers of the at-risk haplotype HapA are shown separately. Two-sided p values corresponding to a standard two-sample test of the difference in the mean values between the MI patients, their various sub-cohorts and the controls are shown.

EXAMPLE 8: HAPLOTYPES ASSOCIATED WITH MI ALSO CONFER RISK OF STROKE AND PAOD.

Because stroke and PAOD are diseases that are closely related to MI (all occur on the basis of atherosclerosis), it was examined whether the SNP haplotype in the FLAP gene that confers risk to MI also conferred risk of stroke and/or PAOD. The 'at risk' haplotype (A4 haplotype) can be defined by the following 4 SNPs: SG13S25 with allele G, SG13S114 with allele T, SG13S89 with allele G, and SG13S32 with allele A.

Table 21 shows that the haplotype A4 increases the risk of having a stroke to a similar extent as it increases the risk of having an MI. The 'at risk' haplotype is carried by 28% of stroke patients and 17% of controls, meaning that the relative risk of having stroke for the carriers of this haplotype is 1.7 (p-value = 5.8×10^{-6}). Although not as significant, the 'at risk' haplotype also confers risk of having PAOD.

Table 21:

		p-val	r	#aff	aff.frq.	#con	con.frq.	info	SG13S25	SG13S106	SG13S114	SG13S89	SG13S30	SG13S32	SG13S42
MI haplotypes															
All MI patients															
	A4	5.3E-07	1.80	1407	0.16	614	0.09	0.82	G		T	G		A	
	B4	1.0E-04	1.87	1388	0.10	612	0.06	0.67	G	G			G		A
Males MI															
	A4	2.5E-08	2.00	864	0.17	614	0.09	0.82	G		T	G		A	
	B4	1.1E-05	2.12	852	0.11	612	0.06	0.67	G	G			G		A
Females MI															
	A4	1.9E-02	1.44	543	0.13	614	0.09	0.73	G		T	G		A	
	B4	7.9E-02	1.45	536	0.08	612	0.06	0.60	G	G			G		A
Replication in stroke															
All stroke patients															
	A4	5.8E-06	1.73	1238	0.15	614	0.09	0.80	G		T	G		A	
	B4	2.3E-04	1.83	1000	0.10	612	0.06	0.71	G	G			G		A
Males stroke															
	A4	1.1E-06	1.91	710	0.17	614	0.09	0.79	G		T	G		A	
	B4	3.1E-05	2.11	574	0.11	612	0.06	0.72	G	G			G		A
Females stroke															
	A4	9.9E-03	1.49	528	0.13	614	0.10	0.74	G		T	G		A	
	B4	6.3E-02	1.47	426	0.08	612	0.06	0.70	G	G			G		A
All stroke excluding MI		8.4E-05	1.65	1054	0.15	614	0.09	0.78	G		T	G		A	
Males stroke excluding MI		6.4E-05	1.78	573	0.16	614	0.09	0.75	G		T	G		A	
Females stroke excluding MI		1.2E-02	1.49	481	0.14	614	0.10	0.72	G		T	G		A	
Cardioembolic stroke		6.6E-04	1.87	248	0.16	614	0.10	0.74	G		T	G		A	

Cardioembolic stroke excluding MI	3.8E-02	1.56	191	0.14	614	0.10	0.70	G		T	G	A
Large vessel stroke	8.0E-02	1.47	150	0.13	614	0.09	0.83	G		T	G	A
Large vessel stroke excluding MI	2.9E-01	1.31	114	0.12	614	0.09	0.80	G		T	G	A
Small vessel stroke	7.2E-04	2.05	166	0.18	614	0.09	0.71	G		T	G	A
Small vessel stroke excluding MI	1.0E-04	2.31	152	0.20	614	0.10	0.71	G		T	G	A
Hemorrhagic stroke	4.4E-02	1.73	97	0.15	614	0.09	0.72	G		T	G	A
Hemorrhagic stroke excluding MI	3.9E-02	1.78	92	0.16	614	0.09	0.71	G		T	G	A
Unknown cause stroke	1.3E-04	1.88	335	0.16	614	0.09	0.75	G		T	G	A
Unknown cause stroke excluding MI	6.5E-04	1.82	297	0.16	614	0.09	0.72	G		T	G	A
MI and stroke together												
All patients												
Best haplo A4	4.1E-07	1.75	2659	0.15	614	0.09	0.82	G		T	G	A
B4	4.1E-05	1.85	2205	0.10	612	0.06	0.70	G	G		G	A
Males												
A4	1.4E-08	1.93	1437	0.17	614	0.09	0.82	G		T	G	A
B4	2.0E-06	2.11	1290	0.11	612	0.06	0.70	G	G		G	A
Females												
A4	3.6E-03	1.47	1024	0.13	614	0.09	0.77	G		T	G	A
B4	2.8E-02	1.48	915	0.08	612	0.06	0.66	G	G		G	A
Patients with both MI and stroke												
A4	6.1E-05	2.10	184	0.18	614	0.09	0.86	G		T	G	A
Replication in PAOD												
All PAOD patients	3.6E-02	1.31	920	0.12	614	0.10	0.84	G		T	G	A
Males PAOD	1.8E-02	1.40	580	0.13	614	0.10	0.84	G		T	G	A
Females PAOD	3.7E-01	1.17	340	0.11	614	0.10	0.83	G		T	G	A
All PAOD excluding MI	1.1E-01	1.24	750	0.12	614	0.10	0.83	G		T	G	A
Males PAOD excluding MI	8.3E-02	1.30	461	0.12	614	0.10	0.83	G		T	G	A
Males PAOD excluding MI and stroke	8.7E-02	1.32	388	0.12	614	0.10	0.83	G		T	G	A

The patient cohorts used in the association analysis shown in Table 21 may include first and second degree relatives.

Table 21, discussed above, shows the results of the haplotype A4 association study using 779 MI patients, 702 stroke patients, 577 PAOD patients and 628

controls. First and second degree relatives were excluded from the patient cohorts. All known cases of MI were removed from the stroke and PAOD cohorts before testing for association. A significant association of the A4 haplotype to stroke was observed, with a relative risk of 1.67 (P value = 0.000095). In addition, it was

5 determined whether the A4 haplotype was primarily associated with a particular sub-phenotype of stroke, and found that both ischemic and hemorrhagic stroke were significantly associated with the A4 haplotype (Table 22).

Table 22: Association of the A4 haplotype to subgroups of stroke

Phenotype (n)	Pat. Frq.	RR	PAR	P-value
Stroke ^a (702)	0.149	1.67	0.116	0.000095
Ischemic (484)	0.148	1.65	0.113	0.00053
TIA (148)	0.137	1.51	0.090	0.058
Hemorrhagic (68)	0.167	1.91	0.153	0.024

^aExcluding known cases of MI.

Finally, the A4 haplotype was less significantly associated with PAOD (Table 21). It should be noted that similar to the stronger association of the A4 haplotype to male MI compared to female MI, it also shows stronger association to male stroke and PAOD (Table 21).

Study population

The stroke and PAOD cohorts used in this study have previously been described (Gretarsdottir, S. *et al. Nat Genet* **35**, 131-8 (2003); Gretarsdottir, S. *et al., Am J Hum Genet* **70**, 593-603 (2002); Gudmundsson, G. *et al., Am J Hum Genet* **70**, 586-92 (2002)). For the stroke linkage analysis, genotypes from 342 male patients with ischemic stroke or TIA that were linked to at least one other male patient within and including 6 meioses in 164 families were used. For the association studies 702 patients with all forms of stroke (n=329 females and n=373 males) and 577 PAOD patients (n=221 females and n=356 males) were analysed. Patients with stroke or PAOD that also had MI were excluded. Controls used for the stroke and PAOD association studies were the same as used in the MI SNP association study (n=628).

The study was approved by the Data Protection Commission of Iceland and the National Bioethics Committee of Iceland. Informed consent was obtained from all study participants. Personal identifiers associated with medical information and blood samples were encrypted with a third party encryption system as previously described (Gulcher, J.R., Kristjansson, K., Gudbjartsson, H. & Stefansson, K., *Eur J Hum Genet* **8**, 739-42 (2000)).

In addition, in an independent linkage study of male patients with ischemic stroke or transient ischemic attack, linkage to the same locus was observed with a LOD score of 1.51 at the same peak marker (FIG. 10), further suggested that a cardiovascular susceptibility factor might reside at this locus.

5

EXAMPLE 9: HAPLOTYPE ASSOCIATION TO FLAP IN A BRITISH COHORT

In an independent study, it was determined whether variants in the FLAP gene also have impact on risk of MI in a population outside Iceland. The four SNPs, defining the A4 haplotype, were typed in a cohort of 750 patients from the United Kingdom who had sporadic MI, and in 728 British population controls. The patients and controls come from 3 separate study cohorts recruited in Leicester and Sheffield. No significant differences were found in the frequency of the haplotype between patients and controls (16.9% versus 15.3%, respectively). However, when an additional 9 SNPs, distributed across the FLAP gene, were typed in the British cohort and searched for other haplotypes that might be associated with MI, two SNPs showed association to MI with a nominally significant P value (data not shown). Moreover, three and four SNP haplotype combinations increased the risk of MI in the British cohort further and the most significant association was observed for a four SNP haplotype with a nominal P value = 0.00037 (Table 23).

20

Table 23 Association of the HapB haplotype to British MI patients

Phenotype (n)	Frq. Pat.	RR	PAR	P-value	P-value ^a
MI (750)	0.075	1.95	0.072	0.00037	0.046
Males (546)	0.075	1.97	0.072	0.00093	ND
Females (204)	0.073	1.90	0.068	0.021	ND

^aP value adjusted for the number of haplotypes tested using 1,000 randomization tests.

Shown are the results for HapB that shows the strongest association in British MI cohort. HapB is defined by the following SNPs: SG13S377, SG13S114, SG13S41 and SG13S35 (that have the following alleles A, A, A and G, respectively. In all three phenotypes shown the same set of n=728 British controls is used and the frequency of HapB in the control cohort is 0.040. Number of patients (n), haplotype frequency in patients (Frq. pat.), relative risk (RR) and population attributed risk (PAR).

This was called haplotype HapB. The haplotype frequency of HapB is 7.5% in the MI patient cohort (carrier frequency 14.4%), compared to 4.0% (carrier frequency 7.8%) in controls, conferring a relative risk of 1.95 (Table 23). This haplotype remained significant after adjusting for all haplotypes tested, using 1000 randomisation steps, with an adjusted P value = 0.046. No other SNP haplotype had an adjusted P value less than 0.05. The two at-risk haplotypes A4 and HapB appear to be mutually exclusive with no instance where the same chromosome carries both haplotypes.

British study population

The method of recruitment of 3 separate cohorts of British subjects has been described previously (Steeds, R., Adams, M., Smith, P., Channer, K. & Samani, N.J., *Thromb Haemost* **79**, 980-4 (1998); Brouillette, S., Singh, R.K., Thompson, J.R., Goodall, A.H. & Samani, N.J., *Arterioscler Thromb Vasc Biol* **23**, 842-6 (2003)). In brief, in the first two cohorts a total of 547 patients included those who were admitted to the coronary care units (CCU) of the Leicester Royal Infirmary, Leicester (July 1993–April 1994) and the Royal Hallamshire Hospital, Sheffield (November 1995–March 1997) and satisfied the World Health Organisation criteria for acute MI in terms of symptoms, elevations in cardiac enzymes or electrocardiographic changes (Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. *Circulation* **59**, 607-9 (1979)). A total of 530 control subjects were recruited in each hospital from adult visitors to patients with non-cardiovascular disease on general medical, surgical, orthopaedic and obstetric wards to provide subjects likely to be representative of the source population from which the subjects originated. Subjects who reported a history of coronary heart disease were excluded.

In the third cohort, 203 subjects were recruited retrospectively from the registries of 3 coronary care units in Leicester. All had suffered an MI according to WHO criteria before the age of 50 years. At the time of participation, patients were at

least 3 months from the acute event. The control cohort comprised 180 subjects with no personal or family history of premature coronary heart disease, matched for age, sex, and current smoking status with the cases. Control subjects were recruited from 3 primary care practices located within the same geographical area. In all cohorts
5 subjects were white of Northern European origin.

DISCUSSION:

These results show that variants of the gene encoding FLAP associate with increased risk of MI and stroke. In the Icelandic cohort, a haplotype that spans the
10 FLAP gene is carried by 30% of all MI patients and almost doubles the risk of MI. These findings were subsequently replicated in an independent cohort of stroke patients. In addition, another haplotype that spans the FLAP gene is associated with MI in a British cohort. Suggestive linkage to chromosome 13q12-13 was observed with several different phenotypes, including female MI, early onset MI of both sexes,
15 and ischemic stroke or TIA in males. However, surprisingly, the strongest haplotype association was observed to males with MI or stroke. Therefore, there may be other variants or haplotypes within the FLAP gene, or in other genes within the linkage region, that also may confer risk to these cardiovascular phenotypes.

These data also show that the at-risk haplotype of the FLAP gene has
20 increased frequency in all subgroups of stroke, including ischemic, TIA, and hemorrhagic stroke. Of interest is that the A4 haplotype confers significantly higher risk of MI and stroke than it does of PAOD. This could be explained by differences in the pathogenesis of these diseases. Unlike PAOD patients who have ischemic legs because of atherosclerotic lesions that are responsible for gradually diminishing blood
25 flow to the legs, the MI and stroke patients have suffered acute events, with disruption of the vessel wall suddenly decreasing blood flow to regions of the heart and the brain.

Association was not found between the A4 haplotype and MI in a British cohort. However, significant association to MI was found with a different variant
30 spanning the FLAP gene. The fact that different haplotypes of the gene are found conferring risk to MI in a second population is not surprising. A common disease like

MI associates with many different mutations or sequence variations, and the frequencies of these disease associated variants may differ between populations. Furthermore, the same mutations may be seen arising on different haplotypic backgrounds.

5

SUMMARY

In summary, it has been found that: MI correlates with genetic variation at FLAP; MI correlates with high expression promoter polymorphism at 5-LO; patients
10 with female MI at-risk FLAP haplotypes have higher levels of serum LTE4; LTE4 levels correlate with CRP levels in serum; and patients with MI at-risk FLAP haplotypes have elevated CRP. In addition, we have shown that isolated neutrophils from MI patients, produce more LTB4 when stimulated with ionomycin compared to controls. Taken together, these results show that increased leukotriene synthesis is a
15 risk factor for MI, and that this risk is driven in part by variants in FLAP and 5-LO genes and are captured in part by measurement of levels of serum LTE4 and CRP. Furthermore, the SNP haplotype in the FLAP gene that confers risk to MI also confers risk of stroke and/or PAOD.

MARKERS UTILIZED HEREIN

5 Table 24: Basepair position of microsatellite markers (start and stop of the amplimersin NCBI sequence assembly build 34 and primer sequences (forward and reverse).

Marker name	forward primer	reverse primer	basepair start position	basepair stop position
DG13S2393	CCTTTGCTTTGTTCTATTCTTT (SEQ ID NO. 4)	TCCATTGCCAGAGTTAAT (SEQ ID NO. 5)	22831401	22831787
DG13S2070	TCCTCATGTCTTCACCTAGAAGC (SEQ ID NO. 6)	CCACTCATGAGGGAGCTGTT (SEQ ID NO. 7)	23020439	23020651
DG13S2071	TGTCACAGGCACACACTCTCT (SEQ ID NO. 8)	GAGTATGGCTGCTGCTCCTC (SEQ ID NO. 9)	23066973	23067076
DG13S2072	ATGGCTCACACTGGCCTAAA (SEQ ID NO. 10)	TGAACAGACCAATAATAGTGACG (SEQ ID NO. 11)	23136964	23137114
DG13S2078	AAGCCACCCTTTAAACAGCA (SEQ ID NO. 12)	GCTGAGGAAGCAACTCCACT (SEQ ID NO. 13)	23591927	23592081
DG13S2079	GCTCTGAATTCCTGGCATA (SEQ ID NO. 14)	TTAGCCCTAGTCCCCTCTCC (SEQ ID NO. 15)	23646974	23647183
DG13S2082	CAAGAGGCCTGCATAAGGAA (SEQ ID NO. 16)	AGATTGCCGGTGGCTTAAAT (SEQ ID NO. 17)	23807898	23808174
DG13S2083	TGTCTGTTCCCGTCTGTCTG (SEQ ID NO. 18)	TTATCCTCTGCCAAATTCC (SEQ ID NO. 19)	23882291	23882532
DG13S2086	GGCATGTATTCACTGCCTGA (SEQ ID NO. 20)	AAACCCATTCTTCTCTCTTAC (SEQ ID NO. 21)	24069346	24069771
DG13S2089	TATGTGTTCCAGCCAGACCTC (SEQ ID NO. 22)	CCCTGCCATGTGCATTAC (SEQ ID NO. 23)	24274920	24275129
DG13S44	CATTTCGGAAGGCAAAGAAA (SEQ ID NO. 24)	TTGCAATGAGGAATGAAGCA (SEQ ID NO. 25)	24413148	24413382
DG13S2095	TCCATTATCCATCTGTTCATTCA (SEQ ID NO. 26)	GAAGAATTAATTGTAGGAGGCAA GA (SEQ ID NO. 27)	24621830	24622121
DG13S46	CTGACATCACCATGATCG (SEQ ID NO. 28)	CATACACAGCCATGTGGAATTA (SEQ ID NO. 29)	24652046	24652291
DG13S2101	ACGGTGATGACGCCTACATT (SEQ ID NO. 30)	TCACATGGACCAATTACCTAGAA (SEQ ID NO. 31)	24863557	24863744
D13S1254	AAATTACTTCACTTGACGATAA CA (SEQ ID NO. 32)	CTATTGGGGACTGCAGAGAG (SEQ ID NO. 33)	25316434	25316657
DG13S55	AGCCAGTGTCCACAAGGAAG (SEQ ID NO. 34)	GAGGGTGAGACACATCTCTGG (SEQ ID NO. 35)	25337471	25337753
DG13S54	AATCGTGCCTCAGTTCATC (SEQ ID NO. 36)	CCACCAGGAACAACACACAC (SEQ ID NO. 37)	25377308	25377463
D13S625	TTGCTCTCCAGCCTGGGC (SEQ ID NO. 38)	TTCTCTGGCTGCCTGCG (SEQ ID NO. 39)	25391207	25391395
DG13S2695	TCCTGCATGAGAAGGAAGT (SEQ ID NO. 40)	CGACATTCAGTGGCTCTT (SEQ ID NO. 41)	25415551	25415807
DG13S1479	TTGATTCCGTGGTCCATTA (SEQ ID NO. 42)	TTATTGGTCGGTGCACCTTT (SEQ ID NO. 43)	25459039	25459368
DG13S2696	GGTGCACCGACCAATAAGT (SEQ ID NO. 44)	CCAGCTTATTCTCTGCCTTC (SEQ ID NO. 45)	25459351	25459478
DG13S1440	GGTAGGTTGAAATGGGCTAACA (SEQ ID NO. 46)	TCATGACAAGGTGTTGGATT (SEQ ID NO. 47)	25520858	25520987
DG13S1890	CCTCCTCTGCCATGAAGCTA (SEQ ID NO. 48)	CTATTGGTCTGCGGGTTGT (SEQ ID NO. 49)	25672727	25673140
DG13S1540	TACTGGGTTATCGCTGACC (SEQ ID NO. 50)	CCAATGGACCTCTTGACAT (SEQ ID NO. 51)	25704358	25704504
DG13S59	TTTCGGCACAGTCCTCAATA (SEQ ID NO. 52)	CAGCTGGGTGTGGTGACAT (SEQ ID NO. 53)	25720194	25720421
DG13S1545	CAGAGAGGAACAGGCAGAGG (SEQ ID NO. 54)	AGTGGCTGGGAAGCCTTATT (SEQ ID NO. 55)	25760018	25760404
DG13S1524	AGGTGAGAGAACAACCTGTCTT (SEQ ID NO. 56)	GCCTTCCTTCTAAGGCAAC (SEQ ID NO. 57)	25843657	25843768

DG13S1529	CTGTAGACTTTATCCCTGACTTAC TG (SEQ ID NO. 58)	CAATGAATGATGAAGATTCCACT C (SEQ ID NO. 59)	26098943	26099063
DG13S1908	TGACACCATGTCTTACTGTTTGC (SEQ ID NO. 60)	GAGGATACAATGAGAACCAAATC TC (SEQ ID NO. 61)	26110282	26110493
DG13S2525	CAGGATCATCAGCCAGGTTT (SEQ ID NO. 62)	GCTGCATGTCTACTAGGCATT (SEQ ID NO. 63)	26123233	26123381
DG13S1546	CCACAGAATGCTCCAAAGGT (SEQ ID NO. 64)	GAGITCAAGTGATGGATGACGA (SEQ ID NO. 65)	26159644	26159995
DG13S1444	CAGATAGATGAATAGGTGGATGG A (SEQ ID NO. 66)	CACTGTTCCAAGTGCTTTGC (SEQ ID NO. 67)	26207544	26207727
DG13S66	TATGCGTTGTGTGTGCTGTG (SEQ ID NO. 68)	GGGCTTAGATTCTTGTAGTGG (SEQ ID NO. 69)	26279746	26279962
DG13S1907	TGTCCAGACTGCCTCCTACA (SEQ ID NO. 70)	TGCAACACCTGGTTCACAAT (SEQ ID NO. 71)	26378401	26378521
DG13S68	TTTGCAGTCTTGTGGAGT (SEQ ID NO. 72)	ACAGTCCGCTCCCTCCTAAT (SEQ ID NO. 73)	26511587	26511825
DG13S69	ATGCTTGGCCCTCAGTTT (SEQ ID NO. 74)	TTGGCAACCCAAGCTAATATG (SEQ ID NO. 75)	26518188	26518483
D13S1250	CTCCACAGTGACAGTGAGG (SEQ ID NO. 76)	GAGAGGTTCCCAATCCC (SEQ ID NO. 77)	26721525	26721686
DG13S574	CAGCTCCTGGCCATATTTCT (SEQ ID NO. 78)	GAGCCATTTCTCTGGGTCTG (SEQ ID NO. 79)	26853541	26853693
DG13S73	GGTCCGTGTCAACCCCTAGA (SEQ ID NO. 80)	CAGGTGTATGGGAGGGAAA (SEQ ID NO. 81)	26878938	26879133
DG13S1532	CGGGAAATGACAGTGAGACC (SEQ ID NO. 82)	TGCCTAGATTCTCCCGTAAG (SEQ ID NO. 83)	26899505	26899652
D13S1242	GTGCCCAGCCAGATTC (SEQ ID NO. 84)	GCCCCAGTCAGGTTT (SEQ ID NO. 85)	26943073	26943316
DG13S576	TTTCTCTCTCCACGGAATGAA (SEQ ID NO. 86)	AACCCATTCTCACAGGGTGA (SEQ ID NO. 87)	27121599	27121797
DG13S1917	AGGAGTGTGGCAGCTTTGAG (SEQ ID NO. 88)	TGGATTTCCCGTGAGTACCAG (SEQ ID NO. 89)	27135092	27135232
D13S217	ATGCTGGGATCACAGGC (SEQ ID NO. 90)	AACCTGGTGGACTTTTGCT (SEQ ID NO. 91)	27169880	27170051
DG13S581	AGCATTTCCAATGGTGCTTT (SEQ ID NO. 92)	CATGTTGATATGCCTGAAGGA (SEQ ID NO. 93)	27318359	27318725
DG13S1471	CACTGTCTGCTGCCACTCAT (SEQ ID NO. 94)	AGAGATTATGTGATGTACCTCTC TAT (SEQ ID NO. 95)	27403303	27403544
DG13S2505	TGATGAAGATCTGGGCGTTA (SEQ ID NO. 96)	TGCCTGTGCTCACTACTCT (SEQ ID NO. 97)	27493479	27493626
D13S120	ATGACCTAGAAATGATACTGGC (SEQ ID NO. 98)	CAGACACCACAACACACATT (SEQ ID NO. 99)	27540983	27541093
D13S1486	TGGTTTAAAAACCTCATGCC (SEQ ID NO. 100)	ATCCCAAACCTGTACTATGTAG G (SEQ ID NO. 101)	27623349	27623496
DG13S1495	CCTTGGCTGTTGTGACTGGT (SEQ ID NO. 102)	CACTCAGGTGGGAGGATCAC (SEQ ID NO. 103)	27668199	27668471
DG13S1845	CACTTTGCCAGTAGCCTTGA (SEQ ID NO. 104)	TTGGGAAAGTTAACCAGAGA (SEQ ID NO. 105)	27788787	27789056
DG13S1030	TTTGGGAAGAGCCATGAGAC (SEQ ID NO. 106)	CTCTGGGCATTGGAGGATTA (SEQ ID NO. 107)	27872811	27873164
DG13S584	GGGAGACAAAGTCAGGTGAGG (SEQ ID NO. 108)	CTGAGTATGGAGTCTTCATCTTA TC (SEQ ID NO. 109)	27924334	27924484
DG13S79	TGCTACTAGATTGACCAACCA (SEQ ID NO. 110)	GACTTGTAAGGATTTAGTGATT CG (SEQ ID NO. 111)	28213368	28213495
DG13S80	GTGGAAGGCCTCTCTCTGTG (SEQ ID NO. 112)	TGCTTCTGAGGGAAAGCAT (SEQ ID NO. 113)	28297121	28297353
DG13S1934	CCTTCAGAGGATTCCCTTTC (SEQ ID NO. 114)	CTGGTTTGACTCCAGCTTCA (SEQ ID NO. 115)	28461787	28462194
DG13S1104	CCTGGCACGGAATAGACACT (SEQ ID NO. 116)	GGCCTCCTTTGCTCTGAAG (SEQ ID NO. 117)	28497694	28498071
DG13S1097	CATCCCTGTGGCTGATTAAGA (SEQ ID NO. 118)	AACAGTTCCAGCCGTTCTA (SEQ ID NO. 119)	28532382	28532543
DG13S1110	TTTCAAAGGAATATCCAAGTGC (SEQ ID NO. 120)	TGGCGTACCATATAAACAGTTCTC (SEQ ID NO. 121)	28547636	28547900
DG13S87	TTCAATGAAGGTGCCGAAGT (SEQ ID NO. 122)	TGTCTATCCCAAAGCTGCAA (SEQ ID NO. 123)	28597688	28597905
DG13S2400	GCTCAGTCCAAGTTCATGCTC (SEQ ID NO. 124)	TGGGATTGGGTCTGGATAC (SEQ ID NO. 125)	28671947	28672231

DG13S3114	CCTACTTTCCATCTCCTCCTTG (SEQ ID NO. 126)	TGGAGTAAGTTGGAGAATTGTTG A (SEQ ID NO. 127)	28678081	28678248
DG13S1111	GCAAGACTCTGTTGAAGAAGAAG A (SEQ ID NO. 128)	TCCTCTGTTTGAGTTTCTCG (SEQ ID NO. 129)	28760422	28760531
DG13S3122	CCTTGGGCAGTCAGAGAAAC (SEQ ID NO. 130)	CCCGTGAAGTCTGAGAGGTG (SEQ ID NO. 131)	28778662	28778906
DG13S1101	AGGCACAGTCGCTCATGTC (SEQ ID NO. 132)	AAACTTTAGCTAATGGTGGTCAA A (SEQ ID NO. 133)	28812542	28812874
D13S1246	GAGCATGTGTGACTTTCATATTC AG (SEQ ID NO. 134)	AGTGCTATTTCATTGCTACAGG (SEQ ID NO. 135)	28903534	28903738
DG13S1103	TTGCTGGATGCTGTTTCTA (SEQ ID NO. 136)	AAAGAGAGAGAGAAAGAGAAAG AAAGA (SEQ ID NO. 137)	28910502	28910765
DG13S3147	AAAGTGGATGCAGTTGAGGTTT (SEQ ID NO. 138)	GCTAGCCATTACAGACAACCAA (SEQ ID NO. 139)	29018341	29018591
DG13S3150	CAGGGCTCCATGTATCCATAA (SEQ ID NO. 140)	CAATCTTTGGCTTTGGGTTT (SEQ ID NO. 141)	29042766	29042948
D13S289	CTGGTTGAGCGGCATT (SEQ ID NO. 142)	TGCAGCCTGGATGACA (SEQ ID NO. 143)	29063702	29063949
DG13S166	CCTATGGAAGCATAGGGAAGAA (SEQ ID NO. 144)	CCCATTCTGAGTCTCCTGAT (SEQ ID NO. 145)	29064359	29064753
DG13S3156	GGGAAATGGAGCTGCTGTTA (SEQ ID NO. 146)	GAGTGGGTGAGTGCAAGGAT (SEQ ID NO. 147)	29111037	29111416
D13S1238	CTCTCAGCAGGCATCCA (SEQ ID NO. 148)	GCCAACGTAATTGACACCA (SEQ ID NO. 149)	29144427	29144579
DG13S2605	TGAAAGGAAGGTCCCTGAGTT (SEQ ID NO. 150)	CCCTGCTTTGCACAAGTTATC (SEQ ID NO. 151)	29145896	29146055
DG13S163	CACATGAGGCTGTATGTGGA (SEQ ID NO. 152)	TGTGCAGGAATGAGAAGTCG (SEQ ID NO. 153)	29177152	29177313
D13S290	CCTTAGGCCCCATAATCT (SEQ ID NO. 154)	CAAATTCCTCAATTGCAAAAT (SEQ ID NO. 155)	29227323	29227512
D13S1229	GGTCATTACAGGAGCCATTC (SEQ ID NO. 156)	CCATTATATTTACCAAGAGGCTG C (SEQ ID NO. 157)	29282262	29282396
DG13S2358	AGTCAAGGCTGACAGGGAAG (SEQ ID NO. 158)	GCTCTCAGCCCTCAATGTGT (SEQ ID NO. 159)	29342275	29342399
DG13S2658	ATTTGGGTTCTCTCCCAAT (SEQ ID NO. 160)	ACAACTCTTGCTGCTGGTG (SEQ ID NO. 161)	29348162	29348426
DG13S1460	TGCCTGGTCATCTACCCATT (SEQ ID NO. 162)	TCTACTGCAGCGCTGATCTT (SEQ ID NO. 163)	29389048	29389297
DG13S2434	TCCTCCAGAAGGTTTGCAT (SEQ ID NO. 164)	TGCAAAAGTTGTTCAAGAGAGACA (SEQ ID NO. 165)	29485254	29485392
DG13S1448	CAGCAGGAAGATGGACAGGT (SEQ ID NO. 166)	CACACTGCATCACACATACCC (SEQ ID NO. 167)	29499404	29499531
D13S1287	TATGCCAGTATGCCTGCT (SEQ ID NO. 168)	GTCACATCAGTCCATTTGC (SEQ ID NO. 169)	29513830	29514063
DG13S2665	GGTTTATGTCTGTGTGTGTGTC (SEQ ID NO. 170)	TGAGGGATGTCAGAGAAATATGC (SEQ ID NO. 171)	29747845	29747984
DG13S1904	TGATGAAATTGCCTAGTGATGC (SEQ ID NO. 172)	GGATCCAATCGTACGCTACC (SEQ ID NO. 173)	29767797	29767922
DG13S1490	ACCTAAACACCACGACTGG (SEQ ID NO. 174)	CAGGTATCGACATTCTTCCAAA (SEQ ID NO. 175)	29908555	29908958
DG13S2637	GGTGATCTAGGGAATTATTTGTC TTC (SEQ ID NO. 176)	TTGGCCACTAAGGTCCAGAT (SEQ ID NO. 177)	29941956	29942120
DG13S96	CCTTTGAGGCTGGATCTGTT (SEQ ID NO. 178)	TTTCCTTATCATTCATTCCCTCA (SEQ ID NO. 179)	30166433	30166650
D13S260	AGATATTGTCTCCGTTCCATGA (SEQ ID NO. 180)	CCCAGATATAAGGACCTGGCTA (SEQ ID NO. 181)	30234833	30234997
DG13S17	TTTAAGCCCTGTGGAATGTATTT (SEQ ID NO. 182)	GACATTGCAGGTCAAGTAGGG (SEQ ID NO. 183)	30288392	30288544
DG13S306	TGCATAAGGCTGGAGACAGA (SEQ ID NO. 184)	CACAGCAGATGGGAGCAAA (SEQ ID NO. 185)	30404049	30404203
DG13S2486	AGCCAGTTGTCTTTCATCCTG (SEQ ID NO. 186)	TGCCTGTGCTTGTATATTCTGTG (SEQ ID NO. 187)	30411508	30411755
DG13S18	GTGCATGTGCATACCAGACC (SEQ ID NO. 188)	GGCAAGATGACCTCTGGAAA (SEQ ID NO. 189)	30456875	30457193
DG13S1062	TTTGTGTTCCAGGTGAGAATTG (SEQ ID NO. 190)	GAACCATATCCCAAGGCACT (SEQ ID NO. 191)	30551596	30551715
DG13S1093	TTGTTCCACATTCATTCTACA (SEQ ID NO. 192)	TTAAACTCGTGGCAAAGACG (SEQ ID NO. 193)	30625918	30626190

DG13S1059	CACCATGCCTGGCTCTTT (SEQ ID NO. 194)	AACCTCTCCAGTTGTGTGGTTG (SEQ ID NO. 195)	30822917	30823246
D13S171	CCTACCATTGACACTCTCAG (SEQ ID NO. 196)	TAGGGCCATCCATTCT (SEQ ID NO. 197)	31051937	31052167
DG13S2359	TCTGTGTATTGTGTA CTCTCT G (SEQ ID NO. 198)	TCACACAATTTGAACCAATCCT (SEQ ID NO. 199)	31073673	31073849
DG13S1092	ACCAAGATATGAAGGCCAAA (SEQ ID NO. 200)	CCTCCAGCTAGAACAATGTGAA (SEQ ID NO. 201)	31113759	31113934
DG13S2629	TGATCATGTCAGCAGCAGAAG (SEQ ID NO. 202)	AGTAACAGGTGAGGGCATGG (SEQ ID NO. 203)	31179791	31179953
DG13S1449	TGTCCATAGCTGTAGCCCTGT (SEQ ID NO. 204)	CTCAATGGGCATCTTTAGGC (SEQ ID NO. 205)	31199228	31199498
DG13S312	CAAACAAACAACAAGCAAACC (SEQ ID NO. 206)	TGGACGTTTCTTTCAGTGAGG (SEQ ID NO. 207)	31280202	31280550
DG13S1511	TGATAACTTACCAGCATGTGAGC (SEQ ID NO. 208)	TCACCTCACCTAAGGATCTGC (SEQ ID NO. 209)	31321562	31321854
DG13S2454	GCTAGCAAATCTCTCAACTCCA (SEQ ID NO. 210)	TCTTCTCCATGCTGCTTCCT (SEQ ID NO. 211)	31352662	31352803
DG13S314	CATGCAATTGCCCAATAGAG (SEQ ID NO. 212)	TTGGGCTTGTCTACCTAGTTCA (SEQ ID NO. 213)	31379760	31380086
DG13S1071	GCTGCACGTATTGTGGTG (SEQ ID NO. 214)	AAACAGCAGAAATGGGAACC (SEQ ID NO. 215)	31447431	31447669
DG13S1068	CCGTGGGCTATCAATTTCTG (SEQ ID NO. 216)	AAGATGCAATCTGGTTTCCAA (SEQ ID NO. 217)	31553333	31553570
DG13S1077	CCCAAGACTGAGGAGGTCAA (SEQ ID NO. 218)	GCTGACGGAGAGGAAAGAGA (SEQ ID NO. 219)	31569360	31569733
DG13S2343	TCACAAAGCAAGCAATCACA (SEQ ID NO. 220)	TGATGGATGCACCATGTTTA (SEQ ID NO. 221)	31653489	31653608
DG13S316	TGAGAAGCCTGGGCATTAAG (SEQ ID NO. 222)	ACAAGCTCATCCAGGAAAG (SEQ ID NO. 223)	31708002	31708244
DG13S1558	AGAGCTGATCTGGCCGAAG (SEQ ID NO. 224)	GGTGGACACAGAATCCACACT (SEQ ID NO. 225)	31986248	31986627
D13S267	GGCCTGAAAGGTATCCTC (SEQ ID NO. 226)	TCCCACCATAAGCACAAG (SEQ ID NO. 227)	32062233	32062380
DG13S1478	TCAACCTAGGATTGGCATTACA (SEQ ID NO. 228)	TCTAGGATTTGTGCCTTTCCA (SEQ ID NO. 229)	32157761	32158137
DG13S1551	ATTCGTGCAGCTGTTTCTGC (SEQ ID NO. 230)	GCATGACATTGTAAATGGAGGA (SEQ ID NO. 231)	32364898	32365153
DG13S1884	GGTGGGAATGTGACTGAA (SEQ ID NO. 232)	CCAGGTACAACATTCTCCTGAT (SEQ ID NO. 233)	32451203	32451315
D13S1293	TGCAGGTGGGAGTCAA (SEQ ID NO. 234)	AAATAACAAGAAGTGACCTTCCT A (SEQ ID NO. 235)	32536337	32536467
DG13S1518	AAAGGATGCATTGCGTTAGAG (SEQ ID NO. 236)	ACTGCTCTGTGCTGTGCTT (SEQ ID NO. 237)	32588965	32589321
D13S620	GTCCACCTAATGGCTCATTC (SEQ ID NO. 238)	CAAGAAGCACTCATGTTTGTG (SEQ ID NO. 239)	32627749	32627947
DG13S1866	AGCCTGTGATTGGCTGAGA (SEQ ID NO. 240)	GGCTTACAGCTGCTCCTTTT (SEQ ID NO. 241)	32633306	32633709
DG13S1927	CCCACAGAGCACTTTGTTAGA (SEQ ID NO. 242)	GCCTCCCTTAAGCTGTTATGC (SEQ ID NO. 243)	32691932	32692304
DG13S1503	CACTCTTTACTGCCAATCACTCC (SEQ ID NO. 244)	GCCGTGTGGGTGTATGAAT (SEQ ID NO. 245)	32699827	32700058
DG13S332	TTGTACCAGGAACCAAAGACAA (SEQ ID NO. 246)	CACAGACAGAGGCACATTGA (SEQ ID NO. 247)	32764576	32764751
DG13S333	GCTCTGGTCACTCCTGCTGT (SEQ ID NO. 248)	CATGCCTGGCTGATTGTTT (SEQ ID NO. 249)	32872275	32872720
D13S220	CCAACATCGGGAAGCTG (SEQ ID NO. 250)	TGCATTCTTTAAGTCCATGTC (SEQ ID NO. 251)	32967602	32967793
DG13S1919	CAGCAACTGACAATCATCCA (SEQ ID NO. 252)	CCTCAATCCTCAGCTCCAAC (SEQ ID NO. 253)	33014255	33014477
DG13S2383	TGATTGGTTCTGTTGTGCTG (SEQ ID NO. 254)	AGCCCAAGGCTCTTGTGAG (SEQ ID NO. 255)	33053369	33053553
DG13S1439	TCCTTCACAGCTTCAAACCTCA (SEQ ID NO. 256)	AGTGAGAAGCTTCCATACTGGT (SEQ ID NO. 257)	33070030	33070264
DG13S335	GCCAACCGTTAGACAAATGA (SEQ ID NO. 258)	CTACATGTGCACCACAACACC (SEQ ID NO. 259)	33102278	33102478
DG13S340	AGTTTATTGCCGCCGAGAG (SEQ ID NO. 260)	ACCCACCACATTCACAAGC (SEQ ID NO. 261)	33124866	33125238

DG13SI496	CGATTGCCATGTCTCTTTGA (SEQ ID NO. 262)	GAGATCTGGCCTGGATTTGT (SEQ ID NO. 263)	33215915	33216066
DG13S347	TCATTGTCAGCACAGAATGAACT (SEQ ID NO. 264)	GGAGGGAGGGAAGAAAGAGA (SEQ ID NO. 265)	33280351	33280688
DG13S339	GGAAGAGGAGATTGACTTGTT (SEQ ID NO. 266)	GGAACACCATCATTCCAACC (SEQ ID NO. 267)	33352425	33352656
DG13SI1926	TACAAGCTCCACCGTCCTTC (SEQ ID NO. 268)	TGAGTTGCTGCCTCTTCAAA (SEQ ID NO. 269)	33388692	33388919
DG13SI1469	TGCTAATGGGCCAAGGAATA (SEQ ID NO. 270)	GCTAAATGTCCTCATGAATAGCC (SEQ ID NO. 271)	33416571	33416940
DG13S351	TGCTCTGCAGACAGATGGTC (SEQ ID NO. 272)	CCTCCGGAGTAGCTGGATTA (SEQ ID NO. 273)	33497762	33498055
DG13S26	GAGACTGGCCCTCATCTTG (SEQ ID NO. 274)	AAGAAGCCAGAGACAAAGAAATA CA (SEQ ID NO. 275)	33584096	33584425
DG13S30	CATCTATCTTTGGATTCACTGGTG (SEQ ID NO. 276)	TGCTCCCAACATCTTACCAG (SEQ ID NO. 277)	33731684	33732071
DG13SI1435	TGCTCTCTGGTCATTCTATGGT (SEQ ID NO. 278)	CATGAATGAGAAGTGATGAATGG (SEQ ID NO. 279)	33762069	33762285
DG13S356	CAGACACTGTAAACTGGCTTCG (SEQ ID NO. 280)	GCCACATTGCTATCAGCGTA (SEQ ID NO. 281)	33908746	33908957
DG13S2316	ATGTGCTGTGGTCCAGATT (SEQ ID NO. 282)	CCTACTACTGCAATTACTCCCTAC C (SEQ ID NO. 283)	33913787	33913954
DG13S357	TGTCATAGGCTTGCGGTATTT (SEQ ID NO. 284)	TTGGTAGGGTCCTTTCCTTT (SEQ ID NO. 285)	33935177	33935378
DG13SI1032	GCCTGCTCACTGTGTTTGA (SEQ ID NO. 286)	CGGTTATCAGAGACTGGTGGT (SEQ ID NO. 287)	33967059	33967269
DG13SI1557	GGCTTATTTTCATGTACGGCTA (SEQ ID NO. 288)	GGTTAAACTCTACTTAGTCTGAT GC (SEQ ID NO. 289)	33996100	33996249
DG13SI1925	GAACCTGTCAGGCACCTCTT (SEQ ID NO. 290)	CCTGAAGCGCTTGTACTGAA (SEQ ID NO. 291)	34079148	34079570
DG13S360	TTGGCTTCTCGCTCTTTCTT (SEQ ID NO. 292)	AGCCATCAGTCACATGCAAA (SEQ ID NO. 293)	34138872	34139221
DG13SI1522	AGATCTCCAGGGCAGAGGAC (SEQ ID NO. 294)	CCTTCTCCCTCCTTCTCTC (SEQ ID NO. 295)	34195314	34195659
DG13S2324	CAGTCAAATGTCTCAACCTTCC (SEQ ID NO. 296)	CTAGCAACATGGCCAAGAAA (SEQ ID NO. 297)	34224040	34224206
DG13SI1517	CGTCATTGATCCCAATCATCT (SEQ ID NO. 298)	GGCTGATAGCCTCCCTTGTA (SEQ ID NO. 299)	34271358	34271587
DG13S364	ACCTTTCAAGCTTCCGGTTT (SEQ ID NO. 300)	TTCATCCGTCATCTATCC (SEQ ID NO. 301)	34323307	34323478
DG13SI1036	TTAAAGTCACTTGTCTGTGGTCA (SEQ ID NO. 302)	TTTGTAGGAATCAAGTCAAATAAT GTA (SEQ ID NO. 303)	34525065	34525280
DG13SI1037	CTTTCGGAAGCTTGAGCCTA (SEQ ID NO. 304)	CCCAAGACCACTGCCATATT (SEQ ID NO. 305)	34616658	34616926
DG13SI1854	TGACAGGTTTGGGTATATTGGA (SEQ ID NO. 306)	TGCTTAATGTAGTGGCAGCA (SEQ ID NO. 307)	34622055	34622151
DG13SI1038	TCCTGCCTTTGTGAATTCCT (SEQ ID NO. 308)	GTTGAATGAGGTGGGCATTA (SEQ ID NO. 309)	34702405	34702738
DG13S2366	TTGGGAATAAATCAGGTGTTGA (SEQ ID NO. 310)	GCAGCAGCTCAGCATTTCTC (SEQ ID NO. 311)	34735455	34735583
DG13SI1039	CCATTTAATCCTCCAGCCATT (SEQ ID NO. 312)	GCTCCACCTTGTTACCCTGA (SEQ ID NO. 313)	34743651	34743817
DG13SI1840	ACAACCTGGAATCTGGACT (SEQ ID NO. 314)	GAAGGAAAGGAAAGGAAAGAAA (SEQ ID NO. 315)	34805466	34805682
DG13S369	TGACAAGACTGAAACTTCATCAG (SEQ ID NO. 316)	GATGCTTGCTTTGGGAGGTA (SEQ ID NO. 317)	34815499	34815755
DG13S2481	CAGGTTAGAGCCCATCCAAG (SEQ ID NO. 318)	AGGCTCAGCTTCATCCACAT (SEQ ID NO. 319)	34867728	34867872
D13S219	AAGCAAATATGCAAAATTGC (SEQ ID NO. 320)	TCCTTCTGTTTCTTGAATAACA (SEQ ID NO. 321)	34956581	34956707
DG13S2351	GGAACAGGTCACAGGTCAT (SEQ ID NO. 322)	GGAAGACTGGGTGGTCACAG (SEQ ID NO. 323)	35099146	35099320
DG13S384	TTCCTTCTGCTTGTGAGCTG (SEQ ID NO. 324)	TACCCTCACCTTCTCATGC (SEQ ID NO. 325)	35499548	35499763
DG13SI1507	GAAGACATTGGCAGGTCTGG (SEQ ID NO. 326)	GAGCCCTCATGTTGGGATAA (SEQ ID NO. 327)	35557977	35558206
DG13SI1512	TTGTTGATTCTCCATTCTGTG (SEQ ID NO. 328)	TCACCTACCTCATCTCATACTCAA A (SEQ ID NO. 329)	35668964	35669201

DG13S1556	TCTTCCGGACAAGTTTCCAA (SEQ ID NO. 330)	TGGGTCAATTCTGGACATTCA (SEQ ID NO. 331)	35791215	35791467
DG13S388	GCAAATGAGGCTGGTAAGGT (SEQ ID NO. 332)	TGCACTGTGGTAGAGGGAAA (SEQ ID NO. 333)	35817061	35817320
DG13S1442	CAACATACTCCTATGCCTAGAAA GAAA (SEQ ID NO. 334)	CTCACCAGGCAGAAAACAGGT (SEQ ID NO. 335)	35842967	35843335
DG13S1045	CCCAATGGCATGCTTCACT (SEQ ID NO. 336)	GGTTCTCCCAGCATTGGTT (SEQ ID NO. 337)	35928180	35928324
DG13S2452	AAGGCCTCTGGGTAGGTAGG (SEQ ID NO. 338)	AAGCAATCCTTATGGGCTCT (SEQ ID NO. 339)	35948528	35948826
DG13S2350	CCAGGTAATCAGAAGCCTCA (SEQ ID NO. 340)	TTCCGTTAAATCCAGCCATC (SEQ ID NO. 341)	36011840	36011961
DG13S2483	CAGGGACTGCAGTGTCTCAA (SEQ ID NO. 342)	ATGCCACATTTGCCTCTCTC (SEQ ID NO. 343)	36027396	36027703
DG13S1100	CCACCTTCCACTTAATACAACT TC (SEQ ID NO. 344)	GAAGCAATCCATTCCAAGAAA (SEQ ID NO. 345)	36056838	36057115
DG13S1501	GTCCTGAGGGTGTCCAGGTA (SEQ ID NO. 346)	GCTGGAGAAGCTCTATTCTGCT (SEQ ID NO. 347)	36215761	36215909
DG13S1868	TGGAGCTATTGCGGTTCTCT (SEQ ID NO. 348)	TCAAATCTCTCTTTCTCCTCCT (SEQ ID NO. 349)	36313203	36313417
DG13S395	CAGTTCCAGCTACGGGAGAA (SEQ ID NO. 350)	CCGCATTTAGGCAAGTCTCA (SEQ ID NO. 351)	36317151	36317507
D13S1491	AAGCACACACAGATGCTAGG (SEQ ID NO. 352)	CCTCAGCCTCCATAATCTCA (SEQ ID NO. 353)	36361442	36361571
DG13S400	GTACAGAGCCCACCTTCTGG (SEQ ID NO. 354)	TCACTATGCTGCAAGGCAAG (SEQ ID NO. 355)	36369862	36370134
D13S894	GGTGCTTGCTGTAAATATAATTG (SEQ ID NO. 356)	CACTACAGCAGATTGCACCA (SEQ ID NO. 357)	36536509	36536706
D13S218	GATTTGAAAATGAGCAGTCC (SEQ ID NO. 358)	GTCGGGCACTACGTTTATCT (SEQ ID NO. 359)	36830331	36830519
DG13S1553	TGGGTGAAGATGCTACCTGA (SEQ ID NO. 360)	CCCTTCTTCTTTCCCTCTC (SEQ ID NO. 361)	36898814	36899040
DG13S411	TGCCAGGTCTGAGTTGTAAGC (SEQ ID NO. 362)	CAGCATGAGACCCTGTCAAA (SEQ ID NO. 363)	36908058	36908265
DG13S1870	GAAAGAAAGAAAGAAAGAAGAA AGAAA (SEQ ID NO. 364)	AATCACCAAACCTGGAAGCA (SEQ ID NO. 365)	36927423	36927632
DG13S1870	GAAAGAAAGAAAGAAAGAAGAA AGAAA (SEQ ID NO. 366)	AATCACCAAACCTGGAAGCA (SEQ ID NO. 367)	36927485	36927632
DG13S39	TCTGAGTTAAACACTTGAGTTGC TG (SEQ ID NO. 368)	CCAGTAAATGGCAGTGTGGTT (SEQ ID NO. 369)	36957292	36957640
DG13S2415	TGTCATGGATATTCTACATAAA CCAA (SEQ ID NO. 370)	TGAAGATGGTTATTGCTTCCTTC (SEQ ID NO. 371)	36984719	36984955
DG13S412	CGCTTTGTTTGGTTTGGTTT (SEQ ID NO. 372)	ATGCAGTTGTCCACATGCT (SEQ ID NO. 373)	37036929	37037137
DG13S414	TCCTGCACTCCAAAGGAAAC (SEQ ID NO. 374)	AACTCTGGTTTAAATTCAGCTTGT C (SEQ ID NO. 375)	37047489	37047713
DG13S1872	TTCTTGAGGGCATAAAGCTGA (SEQ ID NO. 376)	CACACTCACCAGGCACTCTG (SEQ ID NO. 377)	37119505	37119608
DG13S416	CAGGTTTGATGAAGGAAATATGC (SEQ ID NO. 378)	GGGATCCTCTGCATTCTCTAA (SEQ ID NO. 379)	37125983	37126184
DG13S2607	TTTGCCAAATCAACCTTCAG (SEQ ID NO. 380)	CCTGCTTCACACCTCTGACC (SEQ ID NO. 381)	37317455	37317831
DG13S1898	ACTCACACACAACCACCACA (SEQ ID NO. 382)	GCTACTGGTGGGTCGTAAGC (SEQ ID NO. 383)	37318932	37319055
D13S1288	TTGAGAGACCATCACGGC (SEQ ID NO. 384)	CTGGAATAATCAGTTGAATCTA GC (SEQ ID NO. 385)	37321295	37321486
DG13S2567	AGGAAAGCCGAGAAAGCATA (SEQ ID NO. 386)	CATGTATCCACATGCCCAGA (SEQ ID NO. 387)	37416093	37416462
DG13S418	CCTTCAGCGCAGCTACATCT (SEQ ID NO. 388)	AGAACTGCGAGGTCCAAGTG (SEQ ID NO. 389)	37473016	37473380
DG13S419	GGGAGAAAGAGAGGTAGGAAGG (SEQ ID NO. 390)	TICCCAAGTTAGCAGCATCC (SEQ ID NO. 391)	37532947	37533123
DG13S1051	TTCTAGAGGAGTCTATTTCTTAC TGG (SEQ ID NO. 392)	GGAGCTGTCACCTGAGCTTTG (SEQ ID NO. 393)	37694432	37694579
DG13S1841	CCGTGACCTACAGGGAACAT (SEQ ID NO. 394)	GGCATCGGGTGTCTTCTATTC (SEQ ID NO. 395)	37715601	37715829
DG13S1052	AGACCTGCCTGTGTTCTGGT (SEQ ID NO. 396)	GGAGTGAAATAAGTGGAAGTGA (SEQ ID NO. 397)	37831275	37831438

DG13S1053	CATTAAATGAGTCATAAAGGTCA TGG (SEQ ID NO. 398)	AACATTGTTGCTTTGCTGGA (SEQ ID NO. 399)	37935190	37935311
DG13S423	GGCCTTAGCTCAGTTTCTGG (SEQ ID NO. 400)	TGCAAAGACATTGCGGATA (SEQ ID NO. 401)	37941221	37941411
D13S1253	CCTGCATTTGTGTACGTGT (SEQ ID NO. 402)	CAGAGCCGTGGTAGTATATTTT (SEQ ID NO. 403)	37944396	37944533
DG13S2539	GGAACCAAGTCATTGGGTGT (SEQ ID NO. 404)	TTATTGCTCCCTCGTCCAAG (SEQ ID NO. 405)	38050898	38051253
DG13S2509	TGCCTTAAGGTCTATTATTCCTT TC (SEQ ID NO. 406)	ACCAATGCAGGAAGACTCAA (SEQ ID NO. 407)	38067039	38067186
DG13S1863	CTGATGAAAGGACACACATGC (SEQ ID NO. 408)	TGCATTAACATGCAGCTTGAAA (SEQ ID NO. 409)	38092085	38092353
DG13S2510	GTCGTGCAATCCGAGAG (SEQ ID NO. 410)	GGATTCTGCTGGCTCTTCT (SEQ ID NO. 411)	38197807	38198059
DG13S1909	CTGGTGTGGTCAGGAAATGA (SEQ ID NO. 412)	GTGTAAACACATGTGAGTGAGA (SEQ ID NO. 413)	38309328	38309442
DG13S428	TTTGACCATGCTTTCTCTTGA (SEQ ID NO. 414)	GCITGATGACTCCCTGCTGT (SEQ ID NO. 415)	38346716	38347069
DG13S1858	AAGCCATTGAAAGGCAGGTA (SEQ ID NO. 416)	GGGACTTCCGGCTTCTATT (SEQ ID NO. 417)	38371574	38371742
DG13S1911	GGTTTGGGAACCATTTCTCCT (SEQ ID NO. 418)	GCAGAGAAGGGATTACTCCAG (SEQ ID NO. 419)	38475656	38475877
DG13S433	ACTTGACATGGAGCAAGCTG (SEQ ID NO. 420)	AGCTCATCATGCTGTAAGGAG (SEQ ID NO. 421)	38516056	38516191
DG13S2421	CACAGGCTCTCACATTCTCG (SEQ ID NO. 422)	TGACACTCATCCCTCTGCTG (SEQ ID NO. 423)	38534972	38535357
DG13S2375	TGAGTTTCATAAGTTTACTACCTG CTG (SEQ ID NO. 424)	GGCAGGGAGAAAGGACAAAT (SEQ ID NO. 425)	38548257	38548440
D13S1248	TCCCTTATGTGGGATTAGTTGA (SEQ ID NO. 426)	CAGACATGGAAGTGAATTTTTT (SEQ ID NO. 427)	38558005	38558267
DG13S1856	TGTTCCATCTCTTACCCATGT (SEQ ID NO. 428)	TCAATGTTCTTATTGAGTGGGAAA (SEQ ID NO. 429)	38577323	38577506
DG13S435	ATATCCACCCACCCACACAT (SEQ ID NO. 430)	TAGCTCTGAGGGCAGAGACC (SEQ ID NO. 431)	38591043	38591261
DG13S2459	CCGTCTTCTCCACTGAT (SEQ ID NO. 432)	AGAGCACTGAGGGAGCAAAT (SEQ ID NO. 433)	38596056	38596299
DG13S438	AGCTACAGCACGAGGCAGTT (SEQ ID NO. 434)	TTTGAATTGAGTTGCTGTTCTG (SEQ ID NO. 435)	38676957	38677248
DG13S1865	TGTACACCACCAACCATTCTG (SEQ ID NO. 436)	GGGAAGAAAGGCAAATAGCA (SEQ ID NO. 437)	38684800	38684904
DG13S2354	GGATTGGCAATTAGCAGGTC (SEQ ID NO. 438)	GCCTGGTCAAAGATAACAGACG (SEQ ID NO. 439)	38773862	38774026
DG13S2534	CCTGATTAAGCTGGCCTTTG (SEQ ID NO. 440)	ATCCTTCTGGGACCCCTCATC (SEQ ID NO. 441)	38801698	38801951
DG13S1903	GCTTTGCTTCTTCTTGGTG (SEQ ID NO. 442)	CAACATTACGGCCAGTCTCA (SEQ ID NO. 443)	38802843	38803052
DG13S1896	GGTGCATCTGATAAGCCAAA (SEQ ID NO. 444)	GCTGTCTTGGACACAGTGGA (SEQ ID NO. 445)	38815291	38815405
DG13S443	CACCATCATCATCTGGTTGG (SEQ ID NO. 446)	GAGCTATTGAAAGGCAGGA (SEQ ID NO. 447)	38838839	38839093
DG13S445	CCATCCATCTATCCATTATCTCT G (SEQ ID NO. 448)	GGATTATCCTTGCCCTGCT (SEQ ID NO. 449)	38840399	38840584
DG13S447	CTATCATCCATCCATCCTATTG (SEQ ID NO. 450)	TTAGGGCAGCTACCTGGAAA (SEQ ID NO. 451)	38840751	38840928
D13S1233	AGGACTANAGATGAATGCTC (SEQ ID NO. 452)	GACATGACTCCATGTTTGGT (SEQ ID NO. 453)	38875108	38875292
DG13S2320	CCTCACCTTGCAATTCCTG (SEQ ID NO. 454)	CTGACTTGCCTGTTGGCATA (SEQ ID NO. 455)	38957405	38957570
DG13S451	TTTGGATCTTGAAGACCTTT (SEQ ID NO. 456)	TTGTGGCATGTCCTTGGTT (SEQ ID NO. 457)	39032835	39033191
DG13S180	TGTACACTGCAAACATTGCTAAA (SEQ ID NO. 458)	TTGTCTTTCATTATGACGTGTCT (SEQ ID NO. 459)	39233968	39234350
DG13S458	AAGCCTGAAAGGATACACAAA A (SEQ ID NO. 460)	CAGGATCCAGACTTCCAG (SEQ ID NO. 461)	39475899	39476187
DG13S2547	GGTGAATCCCACCCTCATAC (SEQ ID NO. 462)	TTGGTATGTTTCTATTGTTGCAT (SEQ ID NO. 463)	39612492	39612849
D13S244	GAACCACTGAGTTTTTATTAC (SEQ ID NO. 464)	AGACACAGCATATAATACATG (SEQ ID NO. 465)	39665226	39665353

DG13S2435	TGAAGCTTTGTGGCTTGTG (SEQ ID NO. 466)	GACTGAGTCCACAGCCATT (SEQ ID NO. 467)	39863067	39863301
D13S263	CCTGGCCTGTTAGTTTTATTGTT A (SEQ ID NO. 468)	CCCAGTCTTGGGTATGTTTTTA (SEQ ID NO. 469)	39878976	39879126
DG13S188	CCACCATGCAAGAACAGATG (SEQ ID NO. 470)	GCTTTGCACTTGGCTGTCTT (SEQ ID NO. 471)	39935769	39936103
DG13S189	TTGCATGAAGTAAAGTATCCCTG T (SEQ ID NO. 472)	CACAAACCACAAGATGATTGG (SEQ ID NO. 473)	39968676	39969030
DG13S190	GGGCATCATGTCTACAACTCA (SEQ ID NO. 474)	ACCAAGGGCACTTGCTGATA (SEQ ID NO. 475)	40027542	40027801
DG13S2370	AGGATGAAGAGGGAGGAAGG (SEQ ID NO. 476)	CCAGACTGATCTTCCTAATTAGT TG (SEQ ID NO. 477)	40159684	40159812
DG13S196	CCTCCTCTTTCTGCTGCTGT (SEQ ID NO. 478)	AGCCAAAGAACCCAAAGAAAC (SEQ ID NO. 479)	40251445	40251793
DG13S2457	GCCCTACTTTGCCTCAGAAA (SEQ ID NO. 480)	GCAACTCATGCCAGCCTCTA (SEQ ID NO. 481)	40376042	40376447
DG13S2445	AACTGTGTTAATGATGGGCAAA (SEQ ID NO. 482)	AACGAGCGCATGAAACCTAT (SEQ ID NO. 483)	40422793	40423200
DG13S211	CCTGGTCAATTGAACCCAAA (SEQ ID NO. 484)	TGAAGGAAGATAAAGCAGGGTAA (SEQ ID NO. 485)	40434073	40434172
DG13S472	CTCTCTCTGGCCCTCTCTTG (SEQ ID NO. 486)	GGTAACTTGCCATTCTTCTACCA (SEQ ID NO. 487)	40476985	40477395
DG13S207	ACTCCACCTGAAGGGAGAAA (SEQ ID NO. 488)	TGGAAGCCACTAATTGGAGAA (SEQ ID NO. 489)	40545942	40546202
DG13S200	AATGGATGGATACCTCCTTATCA (SEQ ID NO. 490)	CTCATTGTGGCTTTCTGTGC (SEQ ID NO. 491)	40737337	40737570
DG13S198	GTACCCACACCTACCAAGC (SEQ ID NO. 492)	CGTAGCTCACATTCCTCAACA (SEQ ID NO. 493)	40811813	40812059
DG13S215	GGCGAGTGAAAGAGAGGACA (SEQ ID NO. 494)	GGGTGGTAATTCCAGATGA (SEQ ID NO. 495)	40871695	40871992
DG13S221	TCTGCAACAGCCAGAATCAA (SEQ ID NO. 496)	TGCTGTTGGCAACTTCTGTGTC (SEQ ID NO. 497)	41107773	41108117
DG13S219	AGGTGAACCCAGTCCAGCTA (SEQ ID NO. 498)	TCTTAGGCAAAGGAGCCAGT (SEQ ID NO. 499)	41127591	41127734
D13S1270	ACATGAGCACTGGTGACTG (SEQ ID NO. 500)	GGCCTCAAATGTTTAAAGCA (SEQ ID NO. 501)	41161654	41161831
DG13S225	TTCTGGGTGTTGCTATTCC (SEQ ID NO. 502)	TTTCTGTCCAGTCCTGACC (SEQ ID NO. 503)	41212951	41213310
D13S1276	GTTTTGCAGGTCTAGGTCACAC (SEQ ID NO. 504)	AGGATAGCTTGAGCCCG (SEQ ID NO. 505)	41213917	41214090

All references cited herein are incorporated by reference in their entirety.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

- 5 1. A method of treatment for myocardial infarction, stroke or PAOD or susceptibility to myocardial infarction, stroke or PAOD in an individual, comprising administering a leukotriene synthesis inhibitor to the individual in need thereof, in a therapeutically effective amount.
- 10 2. The method of Claim 1, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction, stroke or PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 15 3. The method of Claim 1, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 20 4. The method of Claim 1, wherein the individual has at least one risk factor selected from the group consisting of: a transient ischemic attack; transient monocular blindness; carotid endarterectomy; and asymptomatic carotid stenosis.
- 25 5. The method of Claim 1, wherein the individual has at least one risk factor selected from the group consisting of: claudication, limb ischemia leading to gangrene, ulceration or amputation; and a revascularization procedure.
- 30 6. The method of Claim 1, wherein the individual has an elevated inflammatory marker.

7. The method of Claim 6, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite,
5 interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
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8. The method of Claim 1, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
9. The method of Claim 1, wherein the individual has increased
15 leukotriene synthesis.
10. The method of Claim 1, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.
- 20 11. The method of Claim 1, wherein the individual has had at least one previous transient ischemic attack, transient monocular blindness, or stroke.
12. The method of Claim 1, wherein the individual has asymptomatic
25 carotid stenosis or has had a carotid endarterectomy.
13. The method of Claim 1, wherein the individual has had a revascularization procedure.
- 30 14. The method of Claim 1, wherein the individual has atherosclerosis or who requires treatment (e.g., angioplasty, stents, revascularization procedure) to restore blood flow in arteries.

15. The method of Claim 1, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
16. The method of Claim 1, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.
17. The method of Claim 1, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
18. The method of Claim 1, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.
19. The method of Claim 1, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.

20. The method of Claim 1, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
- 5 21. The method of Claim 20, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
22. The method of Claim 1, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.
- 10 23. The method of Claim 22, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
- 15 24. A method of treatment for acute coronary syndrome in an individual, comprising administering leukotriene synthesis inhibitor to the individual, in a therapeutically effective amount.
- 20 25. The method of Claim 24, wherein the acute coronary syndrome is selected from the group consisting of: unstable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI).
- 25 26. The method of Claim 24, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 30 27. The method of Claim 24, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension;

hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.

- 5 28. The method of Claim 24, wherein the individual has an elevated inflammatory marker.
- 10 29. The method of Claim 28, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 15 30. The method of Claim 24, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
- 20 31. The method of Claim 24, wherein the individual has increased leukotriene synthesis.
32. The method of Claim 24, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.
- 25 33. The method of Claim 24, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries.
- 30 34. The method of Claim 24, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as

- 5 MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-
Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-
dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-
chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-
0-2-acetic acid otherwise known as A-81834, optically pure
enantiomers, salts, chemical derivatives, and analogues.
- 10 35. The method of Claim 24, wherein the leukotriene synthesis inhibitor is
selected from the group consisting of: zileuton, atreleuton, 6-((3-
fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-
methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-
chlorophenyl)methyl)-3-((1,1 dimethylethyl)thio)-alpha, alpha-
dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid
otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-
15 phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide
otherwise known as CJ-13610, their optically pure enantiomers, salts,
chemical derivatives, and analogues.
- 20 36. The method of Claim 24, wherein the leukotriene synthesis inhibitor is
a FLAP inhibitor or antagonist.
37. The method of Claim 24, wherein the leukotriene synthesis inhibitor is
a 5-LO inhibitor or antagonist.
- 25 38. The method of Claim 24, wherein the leukotriene synthesis inhibitor is
a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
39. The method of Claim 24, wherein the leukotriene synthesis inhibitor is
a leukotriene receptor inhibitor or antagonist.

40. The method of Claim 39, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
- 5 41. The method of Claim 24, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.
42. The method of Claim 41, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
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43. A method of treatment for transient ischemic attack, transient monocular blindness or stroke in an individual, comprising administering leukotriene synthesis inhibitor to the individual, in a therapeutically effective amount.
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44. The method of Claim 43, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for stroke; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
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45. The method of Claim 43, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 25
46. The method of Claim 43, wherein the individual has an elevated inflammatory marker.
- 30
47. The method of Claim 46, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum

- 5 amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 10 48. The method of Claim 43, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
49. The method of Claim 43, wherein the individual has increased leukotriene synthesis.
- 15 50. The method of Claim 43, wherein the individual has had at least one previous transient ischemic attack, transient monocular blindness or stroke.
- 20 51. The method of Claim 43, wherein the individual has asymptomatic carotid stenosis or has had a carotid endarterectomy.
- 25 52. The method of Claim 43, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
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53. The method of Claim 43, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.
54. The method of Claim 43, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
55. The method of Claim 43, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.
56. The method of Claim 43, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
57. The method of Claim 43, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
58. The method of Claim 58, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
59. The method of Claim 43, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.

60. The method of Claim 59, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
- 5 61. A method of treatment of PAOD or claudication, comprising administering leukotriene synthesis inhibitor to the individual, in a therapeutically effective amount.
- 10 62. The method of Claim 61, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 15 63. The method of Claim 61, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 20 64. The method of Claim 61, wherein the individual has an elevated inflammatory marker.
- 25 65. The method of Claim 64, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
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66. The method of Claim 61, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
67. The method of Claim 61, wherein the individual has increased leukotriene synthesis.
68. The method of Claim 61, wherein the individual has been diagnosed previously with a condition selected from the group consisting of: PAOD, claudication, and limb ischemia leading to gangrene, ulceration or amputation.
69. The method of Claim 61, wherein the individual has had a vascular or peripheral artery revascularization graft.
70. The method of Claim 61, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
71. The method of Claim 61, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-

phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.

- 5 72. The method of Claim 61, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
73. The method of Claim 61, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.
- 10 74. The method of Claim 61, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
75. The method of Claim 61, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
- 15 76. The method of Claim 75, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
- 20 77. The method of Claim 61, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.
78. The method of Claim 77, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
- 25 79. A method of decreasing risk of a subsequent myocardial infarction or stroke in an individual who has had at least one myocardial infarction or stroke, comprising administering a leukotriene synthesis inhibitor to the individual, in a therapeutically effective amount.
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- 5 80. The method of Claim 79, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction or stroke; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 10 81. The method of Claim 79, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 15 82. The method of Claim 79, wherein the individual has at least one risk factor selected from the group consisting of: a transient ischemic attack; transient monocular blindness; carotid endarterectomy; and asymptomatic carotid stenosis.
- 20 83. The method of Claim 79, wherein the individual has an elevated inflammatory marker.
- 25 84. The method of Claim 83, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 30 85. The method of Claim 79, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.

86. The method of Claim 79, wherein the individual has increased leukotriene synthesis.
87. The method of Claim 79, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.
88. The method of Claim 79, wherein the individual has had at least one previous transient ischemic attack, transient monocular blindness or stroke.
89. The method of Claim 79, wherein the individual has asymptomatic carotid stenosis or has had a carotid endarterectomy.
90. The method of Claim 79, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries.
91. The method of Claim 79, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
92. The method of Claim 79, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-

chlorophenyl)methyl)-3-((1,1dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.

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93. The method of Claim 79, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.

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94. The method of Claim 79, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.

95. The method of Claim 79, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.

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96. The method of Claim 79, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.

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97. The method of Claim 96, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.

98. The method of Claim 79, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.

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99. The method of Claim 98, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.

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100. A method of treatment for atherosclerosis or PAOD in an individual, comprising administering a leukotriene synthesis inhibitor to the individual, in a therapeutically effective amount.
- 5 101. The method of Claim 100, wherein the individual is concurrently treated to restore blood flow in coronary, carotid or peripheral arteries.
102. The method of Claim 100, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a
10 FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
103. The method of Claim 100, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
15
104. The method of Claim 100, wherein the individual has at least one risk factor selected from the group consisting of: claudication, limb ischemia leading to gangrene, ulceration or amputation; and a vascular or peripheral artery revascularization graft.
20
105. The method of Claim 100, wherein the individual has an elevated inflammatory marker.
25
106. The method of Claim 105, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell
30 adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix

metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.

- 5 107. The method of Claim 100, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
108. The method of Claim 100, wherein the individual has increased leukotriene synthesis.
- 10 109. The method of Claim 100, wherein the individual has been diagnosed previously with a condition selected from the group consisting of: claudication, and limb ischemia leading to gangrene, ulceration or amputation.
- 15 110. The method of Claim 100, wherein the individual has had a vascular or peripheral artery revascularization graft.
111. The method of Claim 100, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries.
- 20 112. The method of Claim 100, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
- 25 30

113. The method of Claim 100, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1 dimethylethyl)thio)-alpha, alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.
114. The method of Claim 100, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
115. The method of Claim 100, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.
116. The method of Claim 100, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
117. The method of Claim 100, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
118. The method of Claim 117, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
119. The method of Claim 100, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.

120. The method of Claim 119, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
- 5 121. A method of reducing leukotriene synthesis in an individual, comprising administering a leukotriene synthesis inhibitor to the individual in a therapeutically effective amount.
- 10 122. The method of Claim 121, wherein the individual is concurrently treated to restore blood flow in coronary, carotid or peripheral arteries.
- 15 123. The method of Claim 121, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction, stroke or PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 20 124. The method of Claim 121, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 25 125. The method of Claim 121, wherein the individual has at least one risk factor selected from the group consisting of: a transient ischemic attack; transient monocular blindness; carotid endarterectomy; and asymptomatic carotid stenosis.
- 30 126. The method of Claim 121, wherein the individual has at least one risk factor selected from the group consisting of: claudication, limb ischemia leading to gangrene, ulceration or amputation; and a vascular or peripheral artery revascularization graft.

127. The method of Claim 121, wherein the individual has an elevated inflammatory marker.
- 5 128. The method of Claim 127, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 10 129. The method of Claim 121, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
- 15 130. The method of Claim 121, wherein the individual has increased leukotriene synthesis.
- 20 131. The method of Claim 121, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.
- 25 132. The method of Claim 121, wherein the individual has had at least one previous transient ischemic attack, transient monocular blindness or stroke.
- 30 133. The method of Claim 121, wherein the individual has asymptomatic carotid stenosis or has had a carotid endarterectomy.
134. The method of Claim 121, wherein the individual has had a vascular or peripheral artery revascularization graft.

135. The method of Claim 121, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, revascularization procedure) to restore blood flow in arteries.
- 5 136. The method of Claim 121, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)- α,α -dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)- α -cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
- 10 137. The method of Claim 121, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1-dimethylethyl)thio)- α,α -dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.
- 15 20 25
138. The method of Claim 121, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
- 30 139. The method of Claim 121, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.

140. The method of Claim 121, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
- 5 141. The method of Claim 121, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
- 10 142. The method of Claim 141, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
143. The method of Claim 121, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.
- 15 144. The method of Claim 143, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.
- 20 145. The method of any one of Claims 1-144, wherein the leukotriene synthesis inhibitor is an agent set forth in the Agent Table.
- 25 146. The method of any one of Claims 1-144, wherein the leukotriene synthesis inhibitor is an agent selected from the group consisting of: a complement of a nucleic acid encoding a member of the leukotriene pathway; a binding agent of a member of the leukotriene pathway; an agent that alters expression of a nucleic acid encoding a member of the leukotriene pathway; an agent that alters posttranslational processing of a member of the leukotriene pathway; an agent that alters activity of a polypeptide member of the leukotriene pathway; an agent that alters activity of a leukotriene; an antibody to a leukotriene; and an agent that
- 30 alters interaction among two or more members of the leukotriene pathway.

147. The method of any one of Claims 1-144, wherein the leukotriene synthesis inhibitor is an agent selected from the group consisting of: a FLAP nucleic acid binding agent; a 5-lipoxygenase binding agent; a leukotriene synthetase binding agent; a FLAP nucleic acid binding agent; a 5-lipoxygenase nucleic acid binding agent; a leukotriene synthetase nucleic acid binding agent; a peptidomimetic; a fusion protein; a prodrug; an antibody; an agent that alters FLAP nucleic acid expression; an agent that alters activity of a polypeptide encoded by a FLAP nucleic acid, a 5-lipoxygenase nucleic acid, or a leukotriene synthetase nucleic acid; an agent that alters posttranscriptional processing of a polypeptide encoded by a FLAP nucleic acid, a 5-lipoxygenase nucleic acid or a leukotriene synthetase nucleic acid; an agent that alters interaction of a FLAP nucleic acid with a FLAP nucleic acid binding agent; an agent that alters interaction of a 5-lipoxygenase nucleic acid with a 5-lipoxygenase nucleic acid binding agent; an agent that alters interaction of a leukotriene synthetase nucleic acid with a leukotriene synthetase nucleic acid binding agent; an agent that alters transcription of splicing variants encoded by a FLAP nucleic acid, a 5-lipoxygenase nucleic acid, or a leukotriene synthetase nucleic acid; and ribozymes.
148. A method of assessing an individual for an increased risk of MI, comprising assessing the level of a leukotriene metabolite in the individual, wherein an increased level of leukotriene metabolite is indicative of an increased risk of MI.
149. The method of Claim 148, wherein the leukotriene metabolite is selected from the group consisting of: LTE₄, LTD₄, and LTB₄.
150. The method of Claim 148, wherein the level of the leukotriene metabolite is measured in blood, serum, plasma or urine.

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151. A method of assessing an individual for an increased risk of ACS, comprising assessing the levels of leukotriene metabolites in the individual, wherein an increased level of leukotriene metabolites is indicative of an increased risk of ACS.
152. The method of Claim 151, wherein the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4 and LTB4.
153. The method of Claim 151, wherein the level of the leukotriene metabolite is measured in blood, serum, plasma or urine.
154. A method of assessing an individual for an increased risk of atherosclerosis, comprising assessing the levels of leukotriene metabolites in the individual, wherein an increased level of leukotriene metabolites is indicative of an increased risk of atherosclerosis.
155. The method of Claim 154, wherein the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4 and LTB4.
156. The method of Claim 154, wherein the level of the leukotriene metabolite is measured in blood, serum, plasma or urine.
157. A method of assessing an individual for an increased risk of stroke, transient ischemic attack, transient monocular blindness or asymptomatic carotid stenosis, comprising assessing the level of a leukotriene metabolite in the individual, wherein an increased level of leukotriene metabolites is indicative of an increased risk of stroke, transient ischemic attack, transient monocular blindness or asymptomatic carotid stenosis.
158. The method of Claim 157, wherein the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4 and LTB4.

159. The method of Claim 157, wherein the level of the leukotriene metabolite is measured in blood, serum, plasma or urine.
- 5 160. A method of assessing an individual for an increased risk of PAOD, claudication, or limb ischemia, comprising assessing the level of a leukotriene metabolite in the individual, wherein an increased level of leukotriene metabolites is indicative of an increased risk of PAOD, claudication, or limb ischemia.
- 10 161. The method of Claim 160, wherein the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4 and LTB4.
- 15 162. The method of Claim 160, wherein the level of the leukotriene metabolite is measured in blood, serum, plasma or urine.
163. A method of assessing an individual for an increased risk of MI, comprising:
- 20 i. stimulating production of a leukotriene or a leukotriene metabolite in a test sample from the individual, using a calcium ionophore;
- ii. comparing the level of production of the leukotriene or leukotriene metabolite with a control level,
- 25 wherein a level of production of the leukotriene or leukotriene metabolite that is significantly greater than the control level, is indicative of an increased risk of MI.
164. The method of Claim 163, wherein a level of a leukotriene metabolite is compared, and the leukotriene metabolite is selected from the group consisting of: LTE4, LTD4, and LTB4.
- 30

165. The method of Claim 163, wherein the test sample comprises neutrophils.
166. A method of assessing an individual for an increased risk of ACS,
5 comprising:
 i. stimulating production of a leukotriene or a leukotriene metabolite in a test sample from the individual, using a calcium ionophore;
 ii. comparing the level of production of the leukotriene or
10 leukotriene metabolite with a control level,
wherein a level of production of the leukotriene or leukotriene metabolite that is significantly greater than the control level, is indicative of an increased risk of ACS.
167. The method of Claim 166, wherein a level of a leukotriene metabolite
15 is compared, and the leukotriene metabolite is selected from the group consisting of: LTE₄, LTD₄ and LTB₄.
168. The method of Claim 166, wherein test sample comprises neutrophils.
20
169. A method of assessing an individual for an increased risk of atherosclerosis, comprising:
 i. stimulating production of a leukotriene or a leukotriene
25 leukotriene metabolite in a test sample from the individual, using a calcium ionophore;
 ii. comparing the level of production of the leukotriene or
leukotriene metabolite with a control level,
wherein a level of production of the leukotriene or leukotriene
metabolite that is significantly greater than the control level, is
30 indicative of an increased risk of atherosclerosis.

170. The method of Claim 169, wherein a level of a leukotriene metabolite is compared, and the leukotriene metabolite is selected from the group consisting of: LTE₄, LTD₄ and LTB₄.
- 5 171. The method of Claim 169, wherein the test sample comprises neutrophils.
172. A method of assessing an individual for an increased risk of stroke, transient ischemic attack, transient monocular blindness or
10 asymptomatic carotid stenosis, comprising:
- i. stimulating production of a leukotriene or a leukotriene metabolite in a test sample from the individual, using a calcium ionophore;
 - ii. comparing the level of production of the leukotriene or a
15 leukotriene metabolite with a control level,
- wherein a level of production of the leukotriene or leukotriene metabolite that is significantly greater than the control level, is indicative of an increased risk of stroke, transient ischemic attack, transient monocular blindness or asymptomatic carotid stenosis.
- 20 173. The method of Claim 172, wherein a level of a leukotriene metabolite is compared, and the leukotriene metabolite is selected from the group consisting of: LTE₄, LTD₄ and LTB₄.
- 25 174. The method of Claim 172, wherein test sample comprises neutrophils.
175. A method of assessing an individual for an increased risk of PAOD, claudication, or limb ischemia, comprising:
- i. stimulating production of a leukotriene or a leukotriene
30 metabolite in a test sample from the individual, using a calcium ionophore;

- ii. comparing the level of production of the leukotriene or leukotriene metabolite with a control level, wherein a level of production of the leukotriene or leukotriene metabolite that is significantly greater than the control level, is indicative of an increased risk of PAOD, claudication, or limb ischemia.
- 5
176. The method of Claim 175, wherein a level of a leukotriene metabolite is compared, and the leukotriene metabolite is selected from the group consisting of: LTE₄, LTD₄ and LTB₄.
- 10
177. The method of Claim 175, wherein test sample comprises neutrophils.
178. A method of assessing response to treatment with a leukotriene synthesis inhibitor by an individual in a target population, comprising:
- 15
- a) assessing the level of a leukotriene or leukotriene metabolite in the individual before treatment with a leukotriene synthesis inhibitor;
- b) assessing the level of the leukotriene or leukotriene metabolite in the individual during or after treatment with the leukotriene synthesis inhibitor;
- 20
- c) comparing the level of the leukotriene or leukotriene metabolite before treatment with the level of the leukotriene or leukotriene metabolite during or after treatment,
- 25
- wherein a level of the leukotriene or leukotriene metabolite during or after treatment that is significantly lower than the level of the leukotriene or leukotriene metabolite before treatment, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor.
- 30
179. The method of Claim 106, wherein the level of the leukotriene in steps (a) and (b) is assessed by measurement of *ex vivo* production of the leukotriene in a sample from the individual.

180. A method of assessing response to treatment with a leukotriene synthesis inhibitor by an individual in a target population, comprising:
- a) stimulating production of a leukotriene or a leukotriene metabolite in a first test sample from the individual, using a calcium ionophore, before treatment with a leukotriene synthesis inhibitor;
 - b) stimulating production of a leukotriene or a leukotriene metabolite in a second test sample from the individual, using a calcium ionophore, during or after treatment with the leukotriene synthesis inhibitor;
 - c) comparing the level of production the leukotriene or leukotriene metabolite in the first test sample with the level of production of the leukotriene or leukotriene metabolite in the second test sample,
- wherein a level of the leukotriene or leukotriene metabolite in the second test sample that is significantly lower than the level of the leukotriene or leukotriene metabolite in the first test sample, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor.
181. A method of assessing response to treatment with a leukotriene synthesis inhibitor, by an individual in a target population, comprising:
- a) assessing the level of an inflammatory marker in the individual before treatment with a leukotriene synthesis inhibitor;
 - b) assessing the level of the inflammatory marker in the individual during or after treatment with the leukotriene synthesis inhibitor;
 - c) comparing the level of the inflammatory marker before treatment with the level of the inflammatory marker during or after treatment,

wherein a level of the inflammatory marker during or after treatment that is significantly lower than the level of inflammatory marker before treatment, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor.

- 5 182. The method of Claim 181, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite (*e.g.*, cysteinyl leukotriene 1), interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble
10 intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 15 183. A method of preventing MI, stroke or PAOD, in an individual with an ankle/brachial index less than 0.9, comprising: administering a leukotriene synthesis inhibitor to the individual in need thereof, in a therapeutically effective amount.
- 20 184. The method of Claim 183, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction, stroke or PAOD; an at-risk haplotype in the FLAP gene; a polymorphism in a FLAP nucleic acid; and an at-risk polymorphism in the 5-LO gene promoter.
- 25 185. The method of Claim 183, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated triglycerides; elevated lp(a); obesity; ankle/brachial index (ABI) less than 0.9; and past or current smoker.
- 30 186. The method of Claim 183, wherein the individual has at least one risk factor selected from the group consisting of: a transient ischemic

attack; transient monocular blindness; carotid endarterectomy; and asymptomatic carotid stenosis.

- 5 187. The method of Claim 183, wherein the individual has at least one risk factor selected from the group consisting of: claudication, limb ischemia leading to gangrene, ulceration or amputation; and a revascularization procedure.
- 10 188. The method of Claim 183, wherein the individual has an elevated inflammatory marker.
- 15 189. The method of Claim 188, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, matrix metalloprotease type-9, myeloperoxidase (MPO) and N-tyrosine.
- 20 190. The method of Claim 183, wherein the individual has increased LDL cholesterol and/or decreased HDL cholesterol.
- 25 191. The method of Claim 183, wherein the individual has increased leukotriene synthesis.
192. The method of Claim 183, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.
- 30 193. The method of Claim 183, wherein the individual has had at least one previous transient ischemic attack, transient monocular blindness, or stroke.

194. The method of Claim 183, wherein the individual has asymptomatic carotid stenosis or has had a carotid endarterectomy.
- 5 195. The method of Claim 183, wherein the individual has had a revascularization procedure.
196. The method of Claim 183, wherein the individual has atherosclerosis or who requires treatment (e.g., angioplasty, stents, revascularization
10 procedure) to restore blood flow in arteries.
197. The method of Claim 183, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: 1-((4-chlorophenyl)methyl)-3-
15 ((1,1-dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-0591, (R)-(+)-alpha-cyclopentyl-4-(2-quinolinylmethoxy)-Benzeneacetic acid otherwise known as BAY-x-1005, 3-(3-(1,1-dimethylethylthio-5-(quinoline-2-ylmethoxy)-1-(4-chloromethylphenyl)indole-2-yl)-2,2-dimethylpropionaldehyde oxime-
20 0-2-acetic acid otherwise known as A-81834, optically pure enantiomers, salts, chemical derivatives, and analogues.
198. The method of Claim 183, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: zileuton, atreleuton, 6-((3-
25 fluoro-5-(tetrahydro-4-methoxy-2H-pyran-4yl)phenoxy)methyl)-1-methyl-2(1H)-quinolinone otherwise known as ZD-2138, 1-((4-chlorophenyl)methyl)-3-((1,1 dimethylethyl)thio)-alpha,alpha-dimethyl-5-(2-quinolinylmethoxy)-1H-Indole-2-propanoic acid otherwise known as MK-886, 4-(3-(4-(2-Methyl-imidazol-1-yl)-phenylsulfanyl)-phenyl)-tetrahydro-pyran-4-carboxylic acid amide
30 otherwise known as CJ-13610, their optically pure enantiomers, salts, chemical derivatives, and analogues.

199. The method of Claim 183, wherein the leukotriene synthesis inhibitor is a FLAP inhibitor or antagonist.
- 5 200. The method of Claim 183, wherein the leukotriene synthesis inhibitor is a 5-LO inhibitor or antagonist.
201. The method of Claim 183, wherein the leukotriene synthesis inhibitor is a leukotriene inhibitor or antagonist, or an antibody to a leukotriene.
- 10 202. The method of Claim 183, wherein the leukotriene synthesis inhibitor is a leukotriene receptor inhibitor or antagonist.
203. The method of Claim 202, wherein the leukotriene receptor inhibitor or antagonist is an agent that inhibits or antagonizes a receptor selected from the group consisting of: BLT1, BLT2, CysLTR1, and CysLTR2.
- 15 204. The method of Claim 183, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene biosynthesis pathway.
- 20 205. The method of Claim 204, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, LTC4S, and LTA4H.

ABSTRACT OF THE DISCLOSURE

5 Linkage of myocardial infarction (MI) and a locus on chromosome
13q12 is disclosed. In particular, the FLAP gene within this locus is shown by
genetic association analysis to be a susceptibility gene for MI and ACS, as
well as stroke and PAOD. Pathway targeting for treatment and diagnostic
10 applications in identifying those who are at risk of developing MI, ACS,
stroke or PAOD, in particular are described.

15

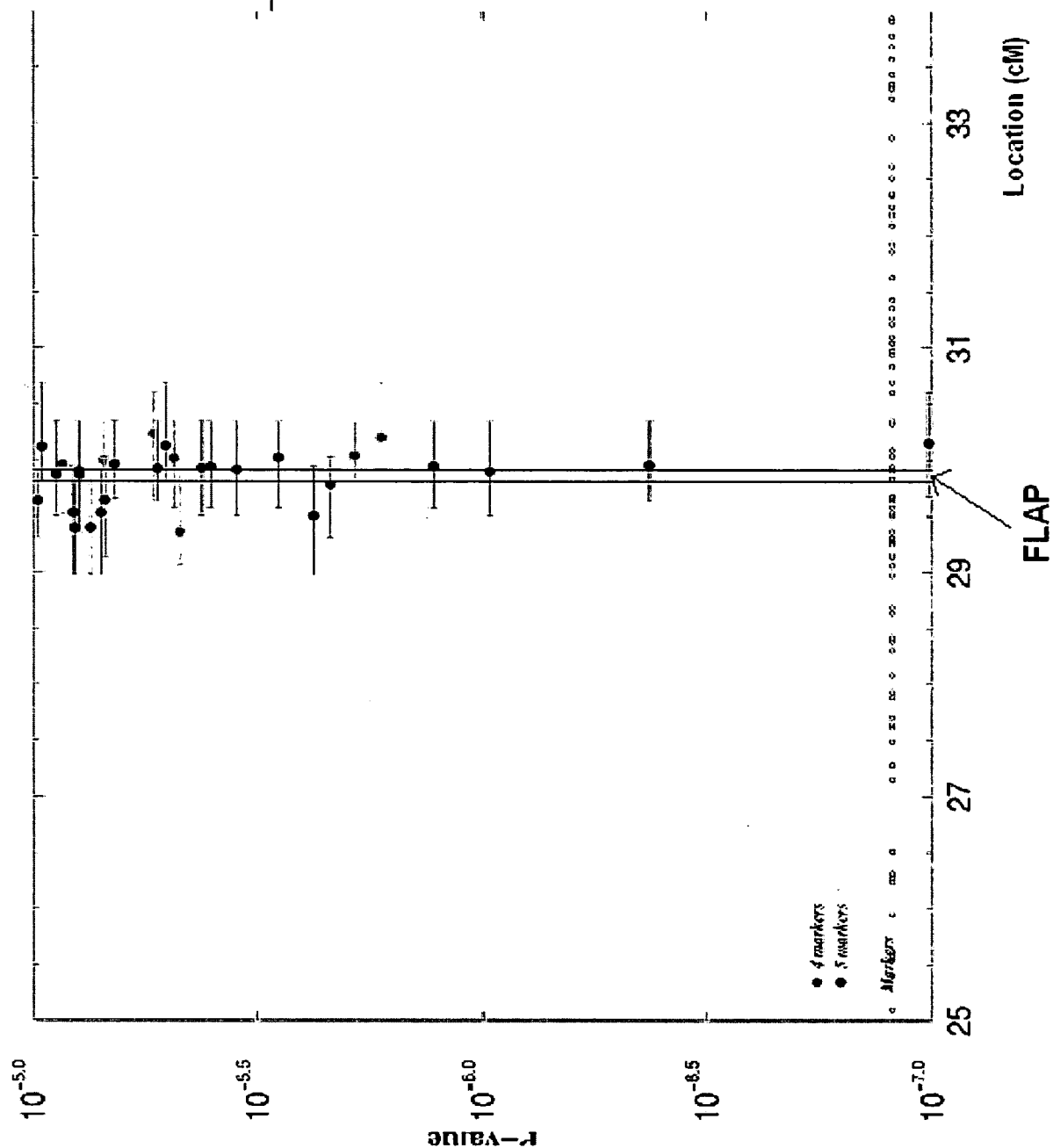


FIG. 1

Haplotypes showing association
(p value < 10⁻⁵) with the disease

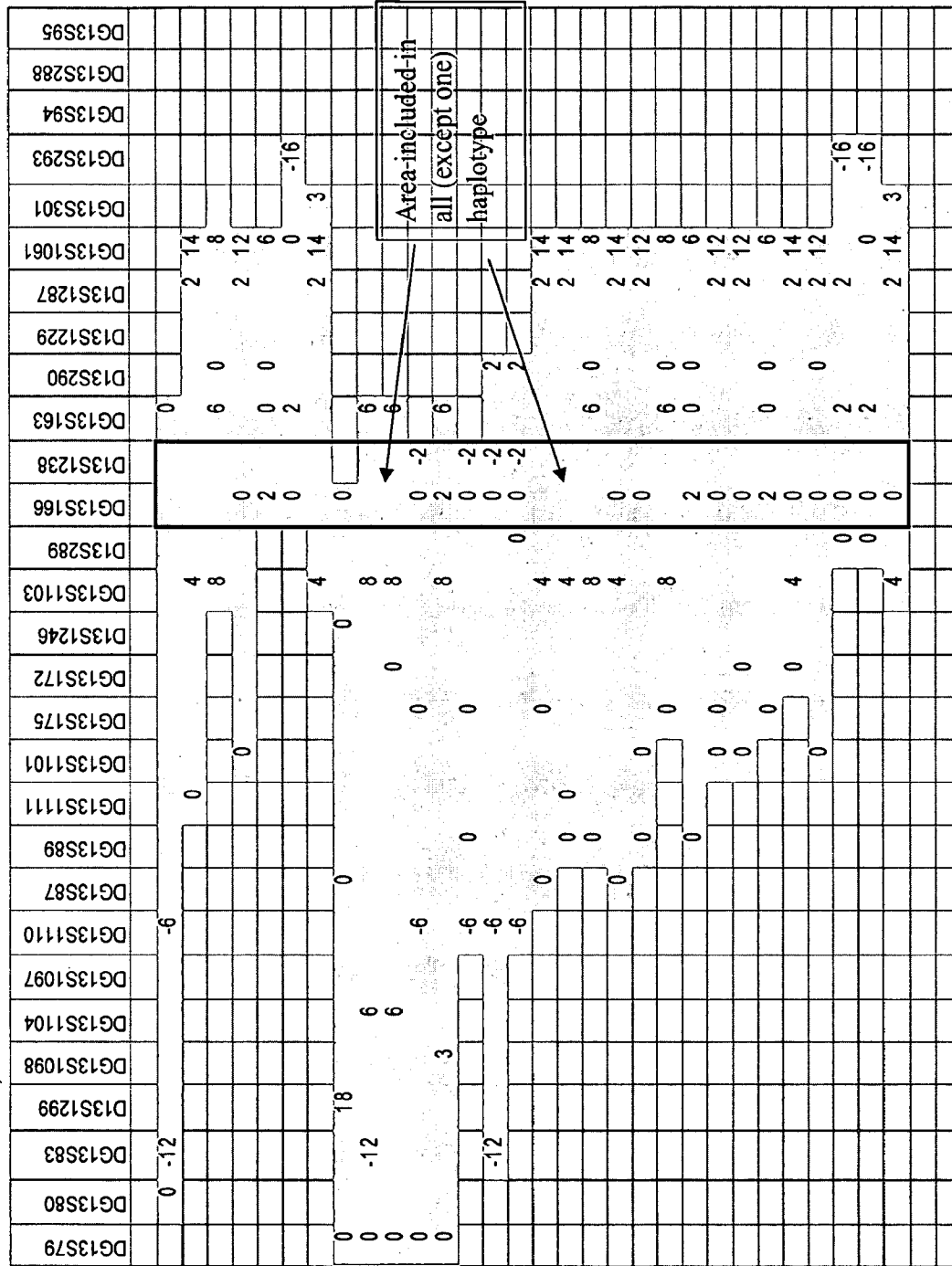


FIG. 2

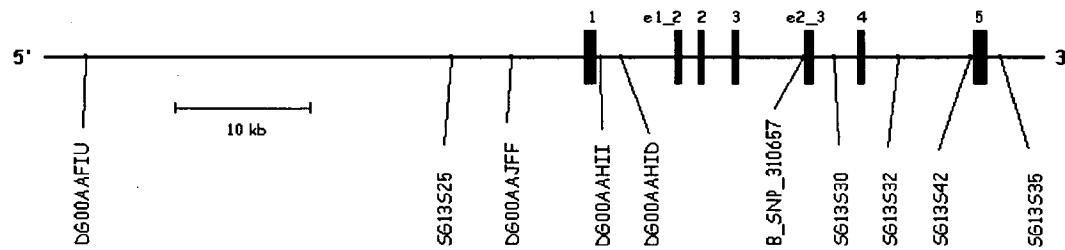


FIG. 3

Amino acid sequence of FLAP (>alox5ap_protein translation NM_01629)

MDQETVGNVLLAIVTLISVVQNGFFAHKVEHESRTQN
GRSFQRTGTLAFERVYTANQNCVDAYPTFLAVLWSAGL
LCSQVPAAAFAGLMYLFVRQKYFVGYL GERTQSTPGYIFGK
RIILFLMSVAGIFNYLIFFFGSDFENYIKTISTTISPLLLIP
(SEQ ID NO: 2)

MRNA of FLAP (NM_001629_mRNA)

Acttcccctctgtacagggcaggtgtgcagctggaggcagagcagtcctctctggggagcctgaagcaaacaatgg
atcaagaaactgtaggcaatgttgctctgttgccatcgtaaccctcatcagcgtggtccagaatggattcttggccataa
agtggagcacgaaagcaggaccagaatgggaggagcttcagaggaccggaacacttgcctttgagcgggtctaca
ctgccaaccagaactgttagatgcgtacccactttcctcgctgtgctctggtctgcggggctactttgcagccaagtcc
tgctgcgttgctggactgatgtactgtttgtgaggcaaaagtactttgtcggttacctaggagagagaacgcagagcacc
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tttcggaagtgaactttgaaaactacataaagacgatctccaccaccatctcccctctacttctcattccctaactctctgctga
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ctgtaaatctattggccatctgggcttcacagcttgagtaaccttgcttttccgggaacaaaatgatgtcatgtcagctccg
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FIG. 4

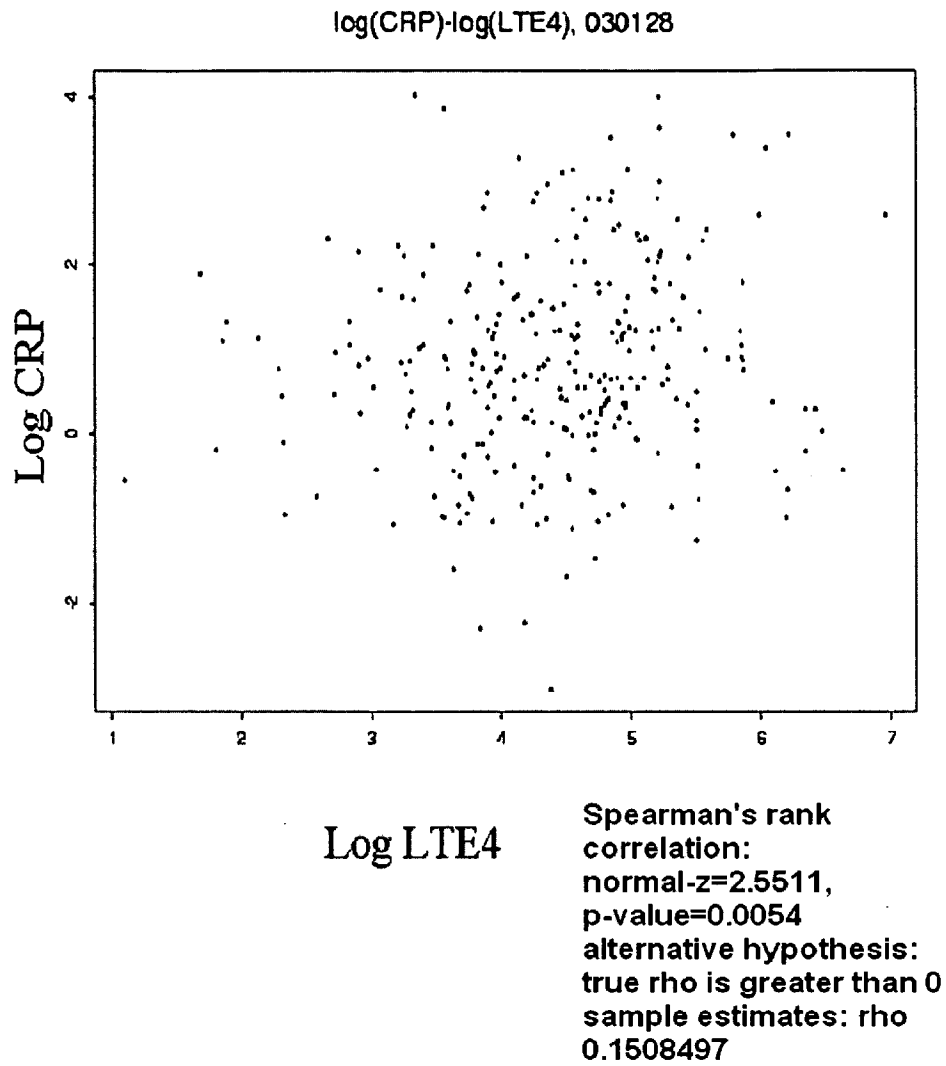


FIG. 5

ID CHROMOSOME 13: 28932001-29146000BP in NCBI build 34.

SQ Sequence 214000 BP SEQ ID NO: 1

GACTAAGATG AATATGCATT CATTACCAA AATCTCATAT TCCCAAAAAG CAGGAAAGGT	60
AGTACAGTGA GATGGATGAT GCCTTCACAT GACTCAGATG TCACGTGTTT CTCACCATTG	120
AGACCCCCAA GGCACCCCCT CCCAGCATTT ACCAGAATGT GTGTGTAAT ATTACAGTG	180
ATTTGTGTAA TTATTTGATT GTTTCTCTTG TATCCTGTAG CAATGAGGGT AGAGATTATA	240
TCCCACCTAC CACTGCAGCT CCAGGATCCA GCTTCACAAA CATTTGTTGA ATGAATGAAT	300
AAGAAAAGAG GACACCCCCA AAGAGGCTGC AAGGGAAAAA GCTACAAAGA CAGAAGCACC	360
AGGAAAAAGT AGGGTCATGT AAGCAAAGC AGGAAAAAAG TTCCATGGTG GGGTGGTCAG	420
CAGTGTCTAA TGCCACGAAG GCACAAAGTA GGATAAAGGT TAAAAATCAG CCTTTGGTTT	480
TGGCAAATAT GAAGCTTATC GGTAGCCTTA GCGAGAACAA TTCCATCAGG GAGCAGAAGC	540
TAAGTGCAGT GGGTTGAGTC ATCAAGCAGG CATAAGGAAG TAGGGATACC CCATTATAAG	600
CTACTCTTTC AAGAAAGCTCA AATCTGAAGG TTAGGAGAAT TAGGTCAGTA GCTAGAAGGA	660
AATGTGGAGT CGAGGGGCTG TTTTCTCTCC CAAGGAGTAT AAAGGTGTAA CGTTGCATGA	720
AACCACTTCA GACAAAGGCC GATATCAATA GAGAAGTTAA AACGCACGCC TCAAGATTG	780
GGAAGGCTTG GGGTTGGGCT TAAAGAGGTA GGAGCATATT TCCTATCCTA GGACAGAGAA	840
TAAAGAAGAA AGGATAGGTT CCCATGGAGA TAAATTTCTA AGTGTTAAAG AAGAGGCTCA	900
GAAAATTCTA GCATGATAGG CTCACTTTTT TCTTTTTCCA TGAAGGAGAT GGCAAAGTCA	960
ACTGACATGA GAAAGGTGAC AATACTGATG GGTGAAGAG CGATGGACAT TTGAAATAAC	1020
TTCTTAGACC AGTAGAGGCT GGAGTTCATA AATCAGAACT GGCTACAGGT TATATATGTT	1080
TTTTTTTTTT TCTCCAACAG CATAAGATAA CAGAGCGAAG TCTGTAGAAA TGAAAGAAGA	1140
GTCAGATGAG GATAGCTGGA GCTAGTGCAA GGAGGGAAGC ACCACGGTGG GAGCCAGGTA	1200
CCCCCTGGAT TTATAATTCA TACTGAATTC CAACAACAGA AGGGCTCTAA GCAGGAGAGT	1260
GACAGATTTC AGAAGACTGA GACACATTTG GTAAAAAATA GTAGGAGGAA AACCTGATTC	1320
TGGAATTAGG GCAGCCAATA GACGGCAGTA TTTTCAGAAA GGAGGGAATG GTCAACAGTG	1380
ACTTTCTAGT CTGGAGCTCA GGAGGAAGAG GCAACTCTAC CTGATGGTAT TAAGATCATG	1440
GAGGTAGCTG AGATCACCTA GCTTGTGTGT GTCAAATGAG AAAAGAAGAA AGAATAGGAG	1500
AAGTTCCTCA GGAACACAGA CATTAAGTGG GGCTGTGGTG ACAACACAAG AAGAGAGGCT	1560
TGCAAAGGAG CCTGAGCAGC TGTCATGAGA GAGGTAGGAT GGTGGACTCG GAGAAGAGGC	1620
AGAAGATGTT CTTAAAGGAA GGACACTGCT GCCAAGTAGT CAGCCAATTG GTGACAAAGA	1680
AAGACCCTGT TGCGAGAAAA AAAGTCAGTG AAGTAGTAGG AACGATGACA GATGACACTG	1740
GGTTGAAGAC TGAGGAGAGA GAAGTGTAAG AGTGGAAGCA GAGGGCAGAC CACTCTTCTG	1800
AGACACTGAA GAGGCATAGT TAGAAATAAA GGGGAGTCGC CAGAAAGGAA TTTGTGGCTA	1860
AGCAAGAGGT TTTCTTTAAG ACTGAAATAC ATAAGCATGA TTAAATGCT GCTGGGATGG	1920
AGTTCACAGA CCTGGAAGAC AGAAGACAAA GCGGATCATC AAGATAGTGG AATTTACTGA	1980
AATGAGAGAG GAAAATCCCA TCCACAGGAA ATGCAGACAT GAGGGAGGGG CCAGAAGGAC	2040
AGTGAAAACA TCAGCAACTG GTCCCCAAC TTCTGAGTGA ATGTGGAGAT ATAATCAGGT	2100
AAAGGACTGC ATCATCTCCC TGGTTAATGA TGGAGTCAGA GAAAAGAGTG TCTTATACAG	2160
AAGTTGTGAT AACTTGGCC GGGCGCAGTG GCTCACGCCT GTAATCTAAG CACTTTGGGA	2220
GGCCAAGGCA GGCAGATCAC CTGAGGTCAG GAGTTCATGA CTGGCCTGGT CAACATGGCA	2280
AAATCCCACC TCTACTAAAA ACAAAGCCT GTAATCCCAG CTACTAGGGA GGCTGAGGCA	2340
GGAGAATCGC TTGAACCCAG GAGGCAGAGG TTGCAGTGAG CCAAGGTCGC ACCACTGTAC	2400
TCCAGCCTGG GCAACAGAGC TAGACTCAGT CTCAAAAAAA AAAAAAAG ATGTATTTAT	2460

FIG. 6.1

TCTCACTGTA TAAATTTCTG TGTAAGAAAT ACTCTCTCAT ATAGAAGTAA ATTTATATAT 2520
AAAATTATAT AGAACCACTA TAAATACTC AGGTTTATAA AATTTATATA TAACTTGTT 2580
GACATATAAA ATTCCATGTA AATGACTATA AAGTACTCTT ATATGAAAAG TATATGAATT 2640
AAATTATATA TCAACTTACT TTTATATTAC AGTATTTTGT TTATACAGAA GTTTATATAG 2700
TGACAATAAA TATTTCTCAA GAACGATTTC ACATAATAGA AGTATAAATT ATCCATTTCC 2760
AATAGTGAAA AAGAAAAGCA GTTCCACACC AGTGACAGGG CTACGAATCT AAGAGGTACA 2820
AAGACTTCAT TCTTAGAGAC ACTGAGGTCA GGGCATGGCC AACACATCTG AAGCTGATAG 2880
AATTGGCGCT GGGTTGGTTG GAGACGGTAC GGTATTACTA TTACAATGGC AGACGCTTGG 2940
CCTTGATAAC TAGCCAATCA GGGGGAAAGA TTCTGGTTTC CTCTGTTATT ATCTGAAC TA 3000
GTGTGTTCCC AAAGGGTTAA GATGGTTTAT GGAAGGCACA AGATCAGCAA ACCATAAAGG 3060
ATTAGCACTA AGAAGGAAGG AAGTAGACCA AGTGTTAATG GCGATGCCAT GTAAGAGCCA 3120
GGTCTGCGAT GTATGTTCTA CATGGTTTGG GGGGTAAAAA AAATGTCAGC CTCCAGAGCA 3180
CAGGGCTTTA AGCCTCAAGT ACTGTTAACA GTAGAGTTTA CTAGTCTACA GCAGGAATTA 3240
CAACCAGTAA TTCTAAGGCC AATTACTCAG GCAAGTTTTA CTAGAACAAG GAAGCTCTGC 3300
TTCGAGGTCA AATCGATTTC TGCATTTATA GAAGCATCTA GATGTTCTCT GTTCAAACAA 3360
TGGGGTAAAA TCCCCACACA TTTTATTTCT GACAGAGTGT TCCCTATATT GCCTGGCCAG 3420
GAGTGATAAC ATTGCTTGGC TATTATTAAT AAAACATTGC TGTGGCTGGG CGCAGTGGCT 3480
CACACCTGTA ATCCTGGCAC TTTGGGAGGC TGAGGCAGGA GGATCACTTA ACTCCAGGAG 3540
TTTGACAGCA GCCTGGGCAA CATAGCAAGA TCCCATCTCT CTAAAAAATT TTAATAATTAG 3600
CTGGGTGTGG TGGCAGACAC CTGTAGTCCC AGCTCCTCAG GAAGCTGAGG TGGGAGGATC 3660
ACTTGAGCCC AAGCAGGTTG AGGCTGCAGC GTGCTGTGAC TGTGCCACTG CACTCCAGCC 3720
TGCGCAACAC ACTGAGAGAG ACTCTGTCTC AAAAAAATAC ATCAAATAAA AATTAAGAAGC 3780
CCATTTCTTT CTTTTGGTAC ATTACAGCCA TGCACTTCAA AGGCTAGCAC AATTATTTTT 3840
CTGCAGTTCT ATATTTAGAT TCTAGTTAGA AGTAACCTAG GACCTTCATG TTAGAGGTGT 3900
CTTTGGCAAA ACTGTTATGT GAGTGAAACG TTTAATCAAT TGAGGATAAA GATGCCTCAT 3960
TGCTAATGAA GATGTGGTTT AAGGATTTTA TGCACCCAGT TCATTTATTA ACAACTTGTT 4020
TAAGCTTTAT TAGCTGGGTC TCTACTTTAT AACTGTGTTT TTTAATTTAC AAGACAATAA 4080
AAATTAAAAT GGTAAATGGG AAACCTATCT TGCTTTTCAA TAAATAATTT ATTTTAATAA 4140
CTTCGTGGGC ATGGTGGCCA AAACATTTTA GCTGTGAAAA TAATTTCAAT TCATATTTTT 4200
TTGGAATCAA TATTAAGAAG TGATATATTC TCAAATGAAA AGTGGACAAA TGATCAGTTA 4260
TAGGACATGA TTAAGAACT AACCATGAGC CACGTGCAGT GGCTCATGCC TGTAATCCCA 4320
GCACTCTGGG AGGCCGCGGT GAGCGGATTG CTTGAGCCCA GGAGTTCAAG ACCAGGCTGG 4380
GCAACATGGC AAAAACCCGG CTCTACTAAA AATGCAAAAA AAAAAAAAAA AAAAAAATT 4440
TAGCTGGGTT TTGGTGGCTT ATGCCTGCAG TCCCAGCTAC TCGGGAGGCT GACTCGGGAG 4500
GCTGAGGCAC AAGAATCATT TGAACCCAGG AGGCAGAGGT TGCAATGAGC TGAGAATACA 4560
CCACTGCACT CCAGCCTGGG CAACAGAGAG AGAGAGACTC AGTCTCAAAA AACAAACAAA 4620
CAACAAACA AACCGCTGCC CTGTGCTTGG AGAGATCTGT TTACCTTTAC CACTAAAGAC 4680
TGTTGGAAGT AAATTTTAGA AGGTTTATAA TACCTAAAAG TAATCACTTC TGTCTTATGA 4740
AAGTTCTGCT TGAGATTTTT CTATTGTGGC CACTAGTGGC AATATTCCAG AAGTCATATT 4800
TAAAGAATAT CTTTAGTGGA TTCAGCAGTT TTTCAAATAT GTACTTTTAT CTCTCCAACA 4860
TTCATGATTG CAATTTTCA AATTAACCTC ATGATATAAA CAACTGTACT CTATGATGCC 4920
TCATAGTACA GAACTGGAG GCAGAAAGAG AAGTTGAATG TCTAAGAATC GGTAATTCTA 4980
AAACTCAACA TAGACCATTG AGCATTAGTG GTTCTAACAA TCCCAGTCA AAATGAGTTG 5040
ATAATGTGTA ACACTTTAGT GAACTAAAGC ATAAAGAACC ATGGTCTCCT AATGCAGCAA 5100

FIG. 6.2

ATTAAACAC ATGATAGCTA CAATTAATGA AGTACATAGT CCTGGCTGGG CACTATGGTA 5160
CGTCCTTTAC ATAGATTATC TCTTAAATTA TTAACCCCGT TTTAGAGATG AGAACATTCG 5220
GGCTCAGGAA GGTTATGTAA GTTATATAAA AATCACAAAA TAAGAGACAG AGCTAAGATT 5280
TGAATCCAAG TGTGACCAGG TTCATATCAA GCTTCCATTT TTGAATTTAT ATTAGAGGTC 5340
AATAACTCAC CTTTGTCTT TTAATAAAT TTTTGGCTCT GTGACCTACA CAGGCAAGCT 5400
GTTATTTACA AACAAACCCAC ACATCTAGAT GGTCACGTGC TCACCGCCCA CTTTTACCAT 5460
CAGGACTCCT AGTGAGCTGT CAAGGGGAAT GCTATAATTT TGGAGGTTCT AAATCTGAGG 5520
GCTTAAGAAA GAAAGAAAT GTAAAAAGCA GGCATTACTC AGGGGCATAG ATTGTCAGGC 5580
AGATCTGTCA TGCTTATAGG TAACCTCCCA GGGCCAAAAA TATATGTGCC CAAACTGCCT 5640
AAATATTTCC TGTCACTTCA TAATACTGCC TGAAATCCTG CCAAATTAGA ACTTCATTTG 5700
TGTTGCTTGT CAATTTTTAA CGCATAAGCA AATCACCTGG AGATCTTGT AAAATGCAA 5760
TTCTGATTAG GTTAGGTCTG GGTCTGCATG TCTGATATGC TTCCAGAGGG CACTGATGCT 5820
GCTGGTCCAT GGACCACACT TAAAGAAGCA AAAAAGATGT CTGATATTTA CTCTCTGGCT 5880
GCCTAGGAGT GCTTCTCATT TAAGTGAGAT CTCTTTGTGC ATCATAATGG GAGGGATGAG 5940
CTGAAAAGCA GCAAATTAAG AGTGAGTTAA GTGTCTACCT CACTTCCCTA CTATCTGTAA 6000
CAAGCAGGTT TGGGCACTGT GGTCAACCAG AAAATTCTTT CCAGGACCAC AACCCTTGAG 6060
ATTATGTTGC AAAGATGCAA GGACAACCTA GAAATAATTT CCAGCACTGG TGGCACTGGA 6120
TGTCTGTCAG TGGTGCTGGT GGCAGGGTCC TATTCAGACT GTGGTTTACC TGCCTGGCCC 6180
GTTTGTTTAT GGGCCATTTT CTGAGTACCA TGGAGCATCG CCCAGCTGAC AAGGGCTTGT 6240
ACTCCACCCT TGGTGCGCAG AAGGGAAGCT TGGCTGCTAC TAAGTTTGGT GCAAAGTAAT 6300
TGTGGTTTTG CCATTAATAT TTGATACAGT GAGTCCCTAC TTTCTCAGG TGAACTAGA 6360
ACTTAAGGGG ACACGCTCAA GTTCTCATT TACAGTACTA AGTTTCAAAA ATCAGCAATT 6420
TTATCAACA CATGCTCTAC AGCAGTGGTC GGCAAACCTT TTCTGTAAGG GGCCAGAGAG 6480
TAAATGTTTT AGAGTTTCTG GGCCACATAT GGTTTCTGTT CCAGCTATAA ACTCTGCCAC 6540
TGTAGGGCAA AAGCAACCCT CCACAATACA TACATGAATA GGTGTGTTCC AAAAAAATT 6600
TATTTGTGGA CCCTGAAATT TGAATTTTCA AAACCTTTCA TGTGTCATGA AATATTCTTT 6660
TGATTTTTTC CCAACCTTTT AAAGATGTAA CAACCATTTT TAGCCTGTAG GCCATATAGA 6720
AACAGGCAGT GGGCTGGGTT TGCTGACCCT TGCTCTGAAG CAATGATATC TCGATCCAAT 6780
TTATACCCAC AAATTTTTCT CTTGAAACC ATGCATTTAA TTCTCATCTC TTCTTACCAT 6840
GACAATAAGA AGTTATTCTA TATAACAAAG AGATTGTACC CACCCAAGCC AGCATTTAGA 6900
TCATGTCATT TGCTTCTCA AAATTTTGGT CTTTATAAAA ATCAATTAAA GCACCTTAAA 6960
AGGTAAGCAG TGATGAAATA TTTGAAATAA TTGGCTAATT AAACATCACC TAAATAGAAA 7020
CTGTGATAAG AACCACAAAT GCGAAAAGGA ATCATGTAGT AACTAATGTG GAGGATATCT 7080
TGGTTTAGAG ATTTGATGAA CACGAGTTTT GATTTAAAAA AATTTGTGCA ATACTCACTG 7140
CTTTGGTGGG GAGCTTGCTA TGCAAGTTGG TAGAAAAATT TATCCTAAAG TCACAGTTCT 7200
CTACCACTCT GGATTTTCTC GAGCTAATA CCATTCCAAA CTATTTTAGG CACAGTTACT 7260
AGTTTCAAGA ATCAGGCAAA TTGCCCTGGT ATTAGCACTG TTCTTTCTGT GGTCAACAAGT 7320
CAAACACTG TGGTGAATAA AATTAGATGA TTTCTTTAGT CTTTCCTTT TCAGCCCCTG 7380
TAGTCAATTT CCAGTGCTCC ATTCAAAGAA AAACCAAAAA TGTCCAGAAT ATAACCTTAT 7440
TTTAAACTT GTTAACCACT GATTTCATT GTTAACCAAA TTTTTTTTTT TTTTTTTTG 7500
AGAATGAATC TCACTCTGTC ACCAGGCTGG AGTGCACTGG CATGATCTTG GTTCACTGCA 7560
ACCTCCGCCT CCTGGGTAAT GGTTCAGCA ATTCTCCTGC CTCAGTCTCC CGAGTAGCTG 7620
GGATTACAGG TGTGCACCCC CACACCCAGC TAATTTTTTT GTACTTTTAG TAGAGATGGG 7680
GTTTCACCAT GTTGGCCGGG CTAGTCTTAA ACTCCTGACC TCGTGATCCG CCCGCCTCGG 7740

FIG. 6.3

CCTCCCAAAG TGCTGGGATT GCAGGCATGA ACCACTGCGC CCAGCCTGTT AACCAAATTT 7800
CTAATCACAC AACTTGAGG CCCAGTAAAT GCCTGCTGAA AAGAGGGTGC TGGTGGTGAG 7860
GCAACTGAGG GGCTAACATA CTGATAGCTG CTGAAATCTT CTACAGCTCT TTCTTGTTAG 7920
AACACTCCAT CACGGCTCCC AGGCCACAC CACATGAAGG AACTTCTAGC TCTCTTGCTT 7980
GCTCTTTACC CAAATGTAGT TAGCAAGTCC TGGGAATAA ACAGCATTGA CACACTTGAA 8040
GAAGACAATT AGGCAAATCC CAACTGCTGT GCTCCTGCAG CTAAAGATGA AGACTCGTCC 8100
ATTGGGCAGT TGATTAATTG TACCTAGAAA ATTAATTTCA ATGGTCCCAT GACAACATAC 8160
GGGCAGTGAA GCTCTAGTGT TCCCCCTGGG TGGAAATCTT CAGGATGTAT AGTCTCCCAT 8220
ACCAGCTCAT CCTCCATT TTCCAGATTG TGGTTCTTCT CTCTTACCTA GTGTGTAGTG 8280
GGCCAAATGG TGGTCCCCCA AAAAGATATG TCCATGTGTT AACCTGGAA ACTGTGGATG 8340
TAACCTTATT TGGAAAAATG GGGCCAGGTG CAGTGGTGTG CATGTGTAGT CCCAGAACTT 8400
TGAGAAGCCA AGGTGGGAGA ATCGTTGGAG CCCAGGAGTT CAAGAACAGC CCAGGCAACA 8460
TATTGAGACC CCCGTCTCTA TAAGCAATAA AAAATTAGCT AGGTGTGGTG GCATGCACCT 8520
GAAGTTCCAG CTACTTGAGA GGCTGAGGCA GAAGGACTGC TCAAGCCCAA GGAGTTCAAAG 8580
GCTGCAGTGA GCTATGATCA TGTCACCCCA CTCCAGCCTG GGTGACAGAG TCAGACTCCC 8640
TGTCTCAGGA GAAAAGAAAA AAAGGTCTTT GTAAATGTAA TAAAGAATCT TGAGATAAGA 8700
TCATCCTGAT TTAGGATGGA CCCTAAATCC AATGACATTT GTCCTTACAA AAGAAAGGTA 8760
GAGGGAAGT TGAGACAGAC ACAGAGGGGA GGGCCTTG TG AAGCAGGAAG CATAGATGCA 8820
GTTACAAGTC AAGGAATGCC AAGGACTGTC TACAACCAGA AGCCAGGAGA GATGCATGGG 8880
ATGATTTCTC CCTCACAGCC TCCAGAACTT CTGGCCTCCA GGACTGTGAA GAATCAATTT 8940
CTGTTGTTTT AAGCCACCAA GTTTGTGTGT CATTGTAT GGCAATGGCA GTATTAGGAC 9000
TCTAATACAC AGTATAAAAA AATAAAAAATA GGGCCAGGCG TGGTGGCTCA GACCTATAAC 9060
CCCAGCACTT TGGGAGGCTA AGGCGGGGAG ATCACTTGAG GTCAGGAGTT TGAGACCAAC 9120
CAGGCCAACA TGGTGAAACC CCATCTCTAT TAAAAATAA AATTAGTTGG GCATGGTGGT 9180
GTGCATCTGT AATCCCAGTT ACTCAGGAGG CTGAGGCAGA AGAATCGCTT GAACCCAGGA 9240
AGTGGAGGTT GTAGTGAATG CCACTGCACT CCAGCCTGGG TGACAGAGCT AGACTCCTTC 9300
ATCCTAGGAC ACAGCCAAGT CTTACGTAGC AAAAGAAGT TGTTAAAGGT CTGTAGTTCT 9360
GCATTAAGCA ACACAGGCAT GTACCTATGA ATTATATGAT TATAAAAGTG CTCGGACAGG 9420
CCCATTTC AA ACTTGCCCTC TTTCCACCA CTGTGTA CTG TTTCTCATT CATAACTAGA 9480
GATTATGTCT TTATATCTG TCAAAAAAGT GAATTTTTGT GGGCTAAGAC ATTATCCCTG 9540
TGTTAAATGC ACCAGTCTTA GTGTAAACAA GCCTAGTTCC TTTTTCATT TGGCTGTCTA 9600
GTATGCATTT GTATATGCTA GGCAGTGTAC TAGGCACCTT AAATACATTA CCTTGTTTAA 9660
CCTCTACAGG ATTCTGGGAG GTAGGCATTA TCCCCATTT ATAGATGAGA AACTGAGAA 9720
GACAATGTTC ATAAGTGC GT CACTTGTCTG AGATGACATA TTTACTAAGT AGCAGAACCA 9780
GGCCTCGAGC TACTCAGTCT GATTTCCAAA GCCCCTGCTC TTAATCACAT CAACTTCTTT 9840
CCTATATCAC CTTTCCCAGA GTGCGCTCTC ATGGATAAAG AGCAGAAGTA TAAGTTACTA 9900
GGCAGCAGAA AACTGTAGAG GTGGGAAGAT TAGATAAAAA ATGTAAATAA GAAGGCTTTA 9960
AGACACCAAA ATCAAATGTA AATACTTTAT AACCTGAATC AGTGCTTGTG TTCATGAGGC 10020
TAGAGGTCGT GCATTTTATC TCTAGGTCTG GTGATGCCAA TCCTGATCTA CAGCCAGCAG 10080
CAACAGTTCC CTAGCCTGCC TAGAAGTTTG TAAATGCATG GGCTTTGGTA GGAGGAAGAC 10140
GAGAGAAAGC AGAACAGATT ATTACAAACC CAGTGCATTC CCCCTTGATG GGTCAACAGC 10200
GATTTCTTTG TAAGTGAAGG ACAGCACACT GGTTTTGATG ACTCACGAGA GAGTAGGAGG 10260
GAAAAAGAAG TCTGAGGCAT TGCCTGGAAG CCTCGCTCTG CTAAACAAG TACACTAATG 10320
GCTCATGCCT GTTACTCCCA GCACTTTGGA AGGCCAAGAT GGGTGGATCA CTTGAGGCCA 10380

FIG. 6.4

GGAGTTTAAG CCCAGCCTGG TCAACATAGC GAGACCTTTT CTCTATTTAA AATAAAGAAG 10440
AAAGAAAAGTA ATAATGATTG AAGTTCTCAT TCTCTACAAA ATTCACCTAT GACTTTCCAA 10500
ATGCTAGTGA AAACCTTTAG GTATTGCAAA ACTGCCTTAA TGCATAACGG GATTCTCATT 10560
TTACTTAGTC TAAGATGACT TTTTCACTTT GAACTTCTGC ATCTTTATGA TCGCTTAGCT 10620
TTCTGACAAG CAATTTCACT AAGTGTATAT CAATTTGCAT CCACACGCTG ACACATAGGG 10680
GTCTACTTAC ATATCCTTCA TGTAATTGAG CTTTGTAAA TCATCTTTCT ACATGGTACA 10740
CTTCTGATTT TGTGTGCAGC TTTCTGTTT AAGCACTGTA TTAAATGCTC TGCTTCCTAC 10800
ACCTTAGGA ACAATGAGAA TAAAAGCGTA ATGTTGGTTA CTTCTTCATA TCAAAGGAAG 10860
TTCATCTCCT GGTATTAAA AGCTATTATT AAATGGCCAT CTTTTGTGC CCCTGTGTTA 10920
AGCACTCTAC CAAGATACCA TTAAATAGAT AAGGGCCACA CTCCATAGAG ATGATGGTTC 10980
TATATTCTGT ATTTTCTGGG GGAGTTCTAA TTTCATGCAA TTCCTTCTTC TTAAATAAAG 11040
GCAATTCTCT AAATATATTA CCTAATGTGC TTTCACTTTC ATATTCTTGT AAGATTTTTT 11100
ACATAAATCA ATTCTCAAAA AATAGTATCA TAGGCCTTTT AAAAATAGTC ATGTTCAAAA 11160
GTCAGGCTCA TGAATAAATG TGTGCATTCA TTACATATAT TTCATAAAT TCAAATTTAA 11220
AAGAATAAGA GTAGCTAGAA GGTGGAAGAA AAATCTTATT CTGATTAGGA ATGCACAATC 11280
ACAAGAAAAT TTGTGATATA TATAGTCATT TTATTCTGTA TTGTTTTATT TTGATTTTGG 11340
TAAGACAAGA AACAATGTAG AAAGTTTGAC AACTTAAAAA AGTAATATGA GTGTGAGAAA 11400
GTCCTCTTCC AGGATTAGCA AAAAAATGGT TTTTTTTTTT TTTTTTCCG AGATGGAGTC 11460
TCGCTCTCTC GCCCAGGCTG GAGTGCAGTG GCGCAATCTT GGCTCACTGC AACCTCCGCC 11520
TCCCGGGTTC AGGTGATTCT CTTGCCTCAG CCTCCCAAGT AGCTGGGACT ACAGGCATGT 11580
GCCACCATGC CCGGCTAATT TTTTTATTT TTAGTAGAGA CGGGGTTTCA CCATGCTGGC 11640
CAGGCTGGTC TTGAACCTCT GACCTTGTA TCTGCCCGCC TTAGCCTCCC AAAGTGCTGG 11700
GATTACAGGC GTGAGCCACC GTACCCAGCC TAAATGGCCA AGTTTTATTA TGGACAATTA 11760
AGCTGTAGAA TAAAAATCTA CTTTAAATAG CTGGCATAGT GCCTAGTGGT TTTGAAGCCA 11820
CAAGCAGGTT TACAAAAAC ATTTAAATCC ATCTGAATCT ACAGAAAACT AAGATTACCT 11880
AAGCAGAAAA TGAAAATAGT TCAGGATTAA GGAAGATTAA CAAATGAAGA GTATATGTAT 11940
TTTAGAAGTA TTACTTTATA TTTTATAGT ATAATAATAA TATTTACGTT CCTACACTTA 12000
TAATGAGTTT CGTATATATA TTAAATAAT TTAATGGATT AGTATGTTA TATTTGCTTT 12060
TAGTAAATTT GGTGTATGAT AAATCAGTT GTCTACATTG TGAGACTACA CCTGAGGCAA 12120
TTTCTGTGTT GATATATACC TGAATAGCAG ATATTACTTG GGAGCAAATA AAATAGCTTC 12180
AGGCCTAATT TTGCAAGTTC ATGATGGGAG AGTAAGCATG ACTTCAAAGA ACTGACTTTG 12240
AGTTAAACT TGAAGAATGA ATGTGACAAC AGCAAGTATA AAACAATGCC AGGCAGAGGT 12300
GGGACTGTTT ATGGGTATCA GGGTAAGTGT GTTGATAAAT GCTCAAAGTA GGAAATACCT 12360
TTCTTCCCC ACACATGTCA GAAAATAACT GCAATAGAAT GCAACGACAT CTCAGAGATA 12420
AAGTGTTCAA CTTAGCTCTC AGAGACCGTT CAGTTACATT TTGTAATGAC ATTGGAATTG 12480
ATTGCATTTT GAAGGCAATT CTAATGCAA AGTCTTCATT TTGTTGATAG AAGCTGGGTT 12540
ATTTATTATG AAATTTCAA AATTAAGTAA AATATCTAAT TAGGATTATA CCAGCAAAGG 12600
CAAATTTAGA ATTCAAGACT TCATGATCCA TGGTAAGATT ATTTAATGC AACTCTGCTA 12660
ATTAAGTAA ATTTCTTTA ACTCTCACAT CTGCCTTTA CTTCTTAAGA CATTTTTCTA 12720
GTATTTCAAC AGAGCAAGAT ATCAGAAGGG TAAATCTCTT ACCAATGAAC TTTGCTAATT 12780
CTTAGTGAAT CCGTTGACCC TGGTGAAGG ATCAGGAACA AAGTGAATGA AATACATTTT 12840
AATACATTTT TGCTTTCTCT AATTCCAAAG ACCACTCTAA AGAATAAGTT ATTTGTGGGT 12900
ATTATCTGAA ACTTGGGATT AAAAGAGACC GTGATTACCC TTCAGGGATT TTGGCAAAAC 12960
TTAAGCCATT TCATCTGAAG AGCAAAGCAA GCCTCCACA CTCTGGCTT ATTCTCACA 13020

FIG. 6.5

TTATCTAGAT ATCTAGCAAC AAAACTCTTG AGTAGTTTGT TAACTACAGA TGCCAAGGGC 13080
TGACAGTTTC ACTTTCAGTT TTCAGAATAT CTTTTGTTTC AGTGGTGTAA GCACACCATC 13140
AGAATCTCTA CTATTTAAAA TAATTAAGTT ATAATTGTAA CTTCCATTAG ATGTAGTACT 13200
TAAAGGAATC TAGAAGACAC AACTCATTAA TTATAGGAAT TTGACTGCAA ATTCTTCTGG 13260
GGGGTCTGAA TTGCAAAGGA GGCATCTTTG TAAGTCAGAC TCAACTCATT ACTCTGTGAT 13320
GCAGGCTCCT CCAAATGGCA GCAGAAACGT ATTACTCTCT AGAAACACTA CAGTAGTGCT 13380
ACAATTTTCTAG GGTCTGTAG AGATAAGGAC AAATTGACAG AAACACATTC TTAGAAGGAC 13440
AGTATCATTT AAAATAAAAA TACTGTCATA ATTGTACACC AGGATAGCTT CTCCATAATA 13500
AATTCTTTAT GATTTTCTGA TTTTATAGAA TCAGAATTGA ACTTTTAAAT GTGAAAAAAA 13560
TGAGAGAATT GTTTCAAAAT AGGACCACAT TTCTGTGTAT AATTTTAAAA GTTTAAAAAT 13620
ATTTGATTAG TAGACTGATA AACTGAAACA TTTTGTATAA GCTTTTCATT ACATACAAAC 13680
CATATAATTT GTAAAAAATT GGAAATTATT CAAAACCTCA CATAACTAAA GTGACCAAAT 13740
AAATACTGGA GAGGAAAGAA AAGGAGTCAA ATGAATCTAG CATTTTCTTT TTTTTTTTTT 13800
TTTTGGAGAA AGGGTCTCAC TGTGCCACCC AGGTGGGAGT GCAATGGCAC GATCATGGCT 13860
CACTGCAGCC TCAACTTTAT GGGCTTAGGT GATCCTCCCA CCTCGGCCCTC CCAAGTAGCA 13920
GGGACTACAG GCATGCGCCA ACACGTCCAG CTAATTTTTT TGGTATTTTT TGCAGAGACG 13980
AGGTTTCACC AGGTTGCCGT GGCTGATCTG GAACTCCTGG TCTCAAGTGA TCTACCCAAC 14040
TCAGCCTCCC AAAGTGCTGG GATTACAGGC GTGAGCCACC GCACCCGGCC TAATCTAGCA 14100
TTTTCTAAAA GGAAGGACCC AGCAGTGAAC GGCAATATCA ATAATCATGT TCAAGACTAT 14160
CAGACATGCA AGCTGGGGAT GAATGGGTGG AAGGGGAAAA TGATGAATAA ATGATGAACA 14220
CAAGTATAGA CCCAGTGGAT TTGAGATGCC CAAGATGCCA GTGAGATATT CAAAGTTTAA 14280
CTCAAAAGCC ACTTCCCATA TGAAATCCTG ACAAACACTC CTACGTCCAA CTGGAATTAA 14340
TTTCTCTTCT GGGCTCCAC AGCACTCTGT ATTTTCTAA TAGCATAACA CTATTTTGTT 14400
TGATAGATATT TCTCTGATAG CATTACTATC TTTCTCTTT ATCACAACCTG TTTGAAGTTC 14460
TTTTGCCTCT TGCATCCACT GTTGCCCAAT CCCACTGCTG GAAGGCTCAT CTTATTAAGT 14520
TCTGTATTCC TAGTGCTAAC ACACTGTCTA CCATAGATGA TGTTCAATAA ATGGTTGCTA 14580
AATGAATTCT CTTGTGATAA TAGCACTATG GCAACATAAT CGACGGTAAA AATTTCTTCT 14640
CAATGTTTAC TTTTAGCAGA ATGCATTCAT TTATCAACTT TCATTGAGAA TATGCTAATT 14700
TCCATGACCC TGCTAGGAAA TAGGAAAATA AAGATGAATG TAATAAGGTG CTCATTCTAC 14760
TGAAAGTCTT GACTAGTGGA GAATTATGGA TCCAACCTTT CATGAAATGC CTTCACTGGT 14820
AAGAATTCTC ATATTTGGAA TAAAAAATGT TATGGGTTGT GCCAAGATAC CTACATACTT 14880
CATAATTTTG TAGAGGGCTG TCCTTACTGC AGAAATGTAT ACTACTATAG TCATATGTGG 14940
AAATCTTTT TATGATGCTA ACTGCATGCT AACCAGACTT TTTAATTTAA TACTTGCATT 15000
AAATAAACCA TGCTAGGAAT CCAGGAATCT AGCTTGGTTT ATTTTCCATA CAATGTACTC 15060
TTTGTAATAT GCATATACTA CATAAAAATT CTATTAATGG CCTCGTACTA AAGATGTGTC 15120
TGTTGGGGAA TCAGTTATTC TGTATAATTT TATCTTAATT GATATATTAA AATCTACCAA 15180
AAATATAAAC TCCGAGTAAA AGTATCTGCA TGGTGTGCAT ATGTTTATTA TTTAAGTGT 15240
CAGCGTATAC ATTTTCATGC CATAAAGTTA TAAATGAAA AAATAGTAGC CTTTTATATT 15300
AAGTTCATGC TTATGTAGTT AGTAAAAACA AGAAAGCAAT TAACATACAA ACCATGATGG 15360
TGGTTAAACT TGCTTCAGTT TGTGTTTTT AAAATTTGAA AGTGAGAAAT ACAGCTCGAA 15420
GTCAGCTCAT ATTTTCAGTA AGTACTGATG AGGATGTACT GGCCCTATTG ACTACGCTGA 15480
CCCCATTTAA ATATTTGTGA GTCTAAAGGT TCATATGACG CTGTTCTTTC ACTCTAGCAA 15540
CAGGCCATAC ATGTCTTACA TAGGGACTCT GTTCAATTCA TTAATACCTC CTGAAGTGCT 15600
CAACATCGTG GTTCATTTAT AGTAGATACT CAATACATAC TCCATTAAT GAATTCTAAG 15660

FIG. 6.6

ATAAACTGTC TGTTACTGAC AGAAATTTTC ACTTAAGGGA GTCTCCGTGG CTGAAGGCAA 15720
TTTTGAAATC CTGTAAAAGA ACCCACTCCT CTCCCCAAGT AATGAAGTTT GTCAGTTTCA 15780
AGCCTGTAAT AAGGTAAGTGA CTTAAATTA ATTTTCTAAT AATACAGTAC TGCTATGTAT 15840
CTAATGTGGG GTTAGTCAAT GATAGGAAAA AAACATAAGA CAGAGTCACA TTTAAAAATG 15900
TGTGCTTAGG TGCATGGTGA CACCTGCCTG TAGTCCAGCT ATTCCAGGGG CTGAGGCAGG 15960
AAGATCCCTT GAGCTCACGA GTTTGAGGCT GCAGTAAGCC ACTGCACTCA GCCTGGGCAA 16020
CAGAGTGAGA CCCTGTCTCT AAAAAAATT CGTTTTAAGT GTGCTCAGGA CATAACAGGA 16080
GCCGCTGGTA ACATGCCATT TCCACTGTGA ATATGGTAAG GACAGAATCC CTGTCTCTAG 16140
GCCCTCTTCC ACTAGTCAAT CTCATCATCA CCATCAAGGC CAACATTGGT ATTCTCTCCT 16200
CTGAGACAAA GTCTTTGACA TTTTCTATAC TATACTATGT CTTCTCTCC CCAAATGCAT 16260
ATACAAATAA AATTTGAATG CTTCTTTCTC CATTTAGTGT AATTTTTTTT ATAACATAGA 16320
CCCAATTTTC AAACCCCAACA ATGGTGGATT TTATTTGATG TATTGTAAAA AGCGCTGGAT 16380
TGAAGTCAAA TGGCTTGGGA GACCTAAATT CTA CTCTCTGC CTGTACCATG AAAGAGACAA 16440
ATCCCAAGGC TTTGCAGGGC TTCAGCTTCC TTGTTTGTAG AATAAAGAAT TATAAAATCA 16500
TCTCTTTTGG TCCTACTGGG CAATAAAAAG CTATGATTCT AAGCCTGTTC CCTTTTCTCA 16560
CCTAAGAATA CAAATTTGAT ACAAAGAGGC CGCAGAATGT GTCAAACACT CCCTGTTGCC 16620
TGGAATTCTC TCTTCCCTTG GGTTCAAGGA TAAAGGTATG TTATTTCTTA AGTCTCCCTT 16680
TGCTTTCTTC TGCTTGCTC GTAAATATTT TTCCATCTTG GCAGTCCTAC ATGTCTTCTC 16740
ACTCTACATG TTTTCCCTAG GTGATGTGAC CCAGCCTGTG GCTTCCACTG CCATCCACAC 16800
ACGTCGCTGC CTCTCTCCAC ATCAGCATCG CAACTATCTC CTGGAAGCTT TCCAAGTGCT 16860
GAACTACAGT AACCTCAACC GAACTGCTGT TCATTCAACC CACAGGCTTG CCCCTCCTCT 16920
GCATCTTTGT GAGAACCTGA GAGTCATCCT AAACCTCTCC TTCCACCTCA CTCCCCACAT 16980
CAAATCGATT ACCAACTTGT GCTGATTTTA TCTTCAAATA CTCTCCAGAA TTGTCGCTGT 17040
CATGGACTGA ATATTTGTGT TCCCCCAAAT TCATATGTCC TAATCCCTGA TGTGACTGTA 17100
TTTAGAGACG TGACCTCTAA GGAGTAATTA AGGTTCAAGT AGGTCAAAGG TGGAGCCCTG 17160
ATCTGATAGG ATCAGTGTCC TTATAAGAAG AGACTAGAGC TGGGCACAGG GGCTCACACC 17220
TGTAATCCCA GTATTTTGGG AGGCTGAGGT GGAAGATCA CTCAAGGAGA GGAGTCTGAG 17280
ACCAGCCTGG GCAACAGAGT GAGACTCCAT CTCTACAAGA AAATAAAATA GTCAGACACA 17340
GTGGTACACA CCTGTGGTCC CAGCTCCTCA GGAGGCTGAG GCAGGAGGAT GGCTTGAGCC 17400
CAGGAATTTG AGGCTGCAGC AAGCTATGAT CACACCTCTG CACTCCAGCC TGGGTGACAG 17460
CATGAGACCC AGTCTCTTTA AAAAAAAAAA AAAAAAAGGC CATATATAGC CCAGAAGAGC 17520
GTCCTCACCA AAACCCAATC CTGATAGCAC CTGGAGGACT TCCAGCCTCC AGAGCTGTGA 17580
GAAAATTTCT GTTGCTTGCA CCGCCCAGTC TGTGGTATTT TGCTGTGGCA GCCCAAGCTG 17640
ACTCATCAGT GACCTTCTCT CTGTTACCGC AGAGTAGCTC ATCATCCTCT CTTCCCTAGA 17700
GTCCAGCCAC TCTCTACAT CTACCTACCT AGCAGTATCA CTGTGGGTTA GAGTCAGATC 17760
ACTGCGGATT AAGTCCTCAT TCTGCCACTG CCTGTGTAAA TCTGAGCAAG TTA CTTAATC 17820
TCTCTGTGTG TCAGTAACCT CCCTGTGAAA TGAGGCTAAT AATAGCAGGG TTGTTTCAAC 17880
AAGGCGATAC ATGCATAATG CTTACAACAC AGCTTGGCAC ATTATAAGCA TTCAACGAAA 17940
AGTGAGCTAC TATTATCTCA TCCGTTATCA GAATAAACCA CCTAAGCCAC AAGGCTGCCC 18000
ACATCATCCT CATGTTTTAA AACACTTCAG TGGGCTCCCC ACCATCAACA GGATAAAGTC 18060
CAAGCTTCCT TAGCATTCTCT TAGAGGCTCC ATATGAATCC CCAAGTTCCA CTACAGGAAC 18120
ACAGGTGAAC TTCCACTCC AACCTCAGGC TCCTTCGTGT CACTCCTCAT CCACATGGAG 18180
GTAAGCAGCA AGAGACTCCG TGCAGTTCCT GGTGGTTCCC TGACCCTCAG GCAGACTCTC 18240
CCCAGCCCTC TGCCTGCAAC GTCCTTGCCC TTTGCTTCCC TTGGCCAGCT CCCATTCAAT 18300

FIG. 6.7

CTCCTTGATT CTGCTTGAA GTTCCCTCT CAGGAAGGCT TTATGAACCT TAGTGTAGGT 18360
TATGAACCCA TCTTTGCTCC TTTCATACCT TTGCAAGCC TTTATTTATT ATGACACTTA 18420
ACCATATCA TACTGAAGTG ACCTGTTGGT GTGTCTTTGT TCCCCACTAG ACAGAAACT 18480
CAAGATCAGA GACCAGTTCT TGTTCTTTTT TTTTTTTTTT TTTTTTTTTT TTGTATCACA 18540
GTGTTTAGCA GCCTGCTATA TGGTAAATGT CAGTAAATGT TCCACAACT GAATGGAATT 18600
GAGCTCTGGA ATCTAGACCA TCTTTTCCAT ACCCATCACT CCTGTCTTAG TTGAAGTCCT 18660
TATTTCCCAT TTGAAGCAAT GCAAAGGATT TCCTAACTCT AATCTCTCTT TTCTTCACAC 18720
CATCCTTTAA ACAGCCGACA GAATGGTCAT CCTAAAGCAC ATATATCCTA TCTTACATAT 18780
CCTAGATTCTG GAACCTCTCT GGGCTTCTCA CCATATAAGA AGAAAGTCTA ACCTCCTTAG 18840
CAAGGTGCAT AGGTCTTCAA TGGGCTCCAC CTCACCTCTC TATATATACC TATACTCTTG 18900
CTACACTAAA CTCTTTCTT ACTGTTGCTG GAACAAGTTC AACGCTTTC AACCTCCCTG 18960
ACTTTGCATA TGCAGTTCAT TCTGTCAGGA ATGCCCTTCT CTCTTATGCC TGGGATATTC 19020
TCATTCATTC CATATGACCT ATTTCAATAAG TCACTCCTTA ATGAAGCCTT TCTTAGATAT 19080
CCACTGGGGC AATCAGCTGC TTGCTCCTGT TTCCACAGCA CATTGTTTAC ACAGATAGCA 19140
CAGGACTTAC CACAAGTTAT TATAATTTTG TCTGTCTTGC CCATTTGAAT CCAAGGGCAA 19200
GGACGGAATC ATTCTCATCT TTGTATGTCC TGGGAAGTAG AACTGTACCT GAGACATAAT 19260
AAACACTTGA TATGTTTGTG ATTTTAAAT AAGTTAATGA ACGGAATGGC TAGAAAAAGT 19320
GAGAAGAAAC TCTGGCTTAC TGTATATCAT ACTGTCATAC TAAAAATATA TACTGAAGAC 19380
AGAATCACAT TATATCATCA CTTTTCACGC TATAGGCCAT GATCCATTAT GAAAAAGAGG 19440
ATAGTAAAAA AATCACAGGG CACAATTTTT GTTTCTGTCA CACACATGTG TACCTGTATA 19500
TTGGACTGGA ATGTAAACG CATGTTCCAT TGTAAGACGT GGTTTTAAAA GAGGCTTGGA 19560
AAACACTGCA TATGGTCATT TCTTAGTTTA GTACAATTTA TTATTTTCGT AATAACCTCA 19620
GCTATAATAT AAGTCTACCA TGAAGCATT TGGGGAGATT AAATGAGATG TGAAGAGTAA 19680
ATGTGTTAGA TAGACTGAAT TCATATCATA GCTTGCTCTG ATACTTTACA AAACATTTAA 19740
CCTTACCCAC AAGTTTGTAG TTCCTCACTA AAGTCACCCT GAGGACAGTA ATGGGATCTT 19800
CCTCACAGAG TATTGTGAGG AATACATAAG AGAACGTACG TAAATGCCTG GCACCTAGTA 19860
TTTATTCAAT AAATCTTAGC AATGATGATG ATAACAACAT GGTACCTGGC ACATAAGAGA 19920
GTAAAAAATT AGTTTCTTCA GTCAAATGTG CTTACATTGA TAGTTGATAC TAACTGGGGT 19980
TAAAAGGTCA TTGCTGGCAT CTCAGAAAGA TAGATTACAG TGAAATAAAA AATGACTACT 20040
GCTTAAAAATG AATGAAGACT TATTTACAAA GTCATGTTCA TCTGGTACAA TAATGAAGTC 20100
GCTCAATTGG GAGAAAATGA CAAATAATAC AAGTGAATAT ACAATCTTAC TTAAGACGAA 20160
AGAAATAGGA CACCAGGCTA ACTATCAGTC TCCTAAACCA CAACTTTATT TCTGATACAA 20220
AGAGACAGTG AGACAATCAG GGCTTCCCTC AAATAAATTA CTTAATCTCT CTTCAATTCA 20280
GTTTTGCATC TGTAATATA AATAACTACA ATTTACAGT ATTTCCATTT AAAAAGTTCT 20340
AGTGCAACAT CAGAAACAAG AACTTAGTAG GTGTTCAAAA AGAAATATAA GTTCTGCTTT 20400
GTTAGCCAGC AAATAGTTGC CTGTTTCTAG CCCTCACTTC TTTTCTCCTA AATCCCTATA 20460
TTGCATTTAT TTAACCTAAA GTGCTGGATG TGGCACTACG AGAAAGAAAA AGATATTTGG 20520
TAATCTTGTT AAAATCATTG GACATCCCAG GCTATCTGGA ATCACCTTGG GCTCACAGTT 20580
AGACATCAGC TATGGCTTGT TTTATTTAAA AATTCATCCA CTGATGCATG ATAATGGAAT 20640
TCACAGGAGA GCAATTTACC AAAAAAAGA AATTTATTGA TTTATAATGT GAGATATTAA 20700
TTTAGCCACA AATATTTATT GAGCATCTCC TACATGCCAG GGAATGGACT ATATATGGCA 20760
GGAAACAGA TACCAATCAT TTATATCAGG CATTTTTTTC TAATAGAAGG ATATTCGCAG 20820
GAGACAATGC ATAGCACCAT GCCTTGACAG TAACAGACAT TTAATAACTA TTAGTTGAAT 20880
AAAATTGGAG ACTAGAATGA TACATAAAGA GGCAAGAAAG AGCAAAGATA AGCCTTCTG 20940

FIG. 6.8

AGAATTTCTA TCATGTTTTG CTCAATAGCT TGTCTTTATC CACTGCTTGT ATTTTTCAT 21000
GTAGCTAATC CTCATTGGTC GTTAGAATTG AGACACCCTT TCCTTGAAAT CAGGAGCTAT 21060
AGGAGGCCAT TCTTCCTACT GGGCATTTC TTTCTGGGAC AGGGTCTCAC TCTGTCACCT 21120
AGGCTGGAGT GCATCATAGC TCACTATAAC CTTGAAGTCC TGGGCTCAAG GAATCCTCTT 21180
GCCAAAGAGG TGGGATTACA GGCATGAGTC ACCATGCCAG CCTATTTGGC ATTTCTACTG 21240
TAGACAAAGC AGACTTACAG CAGTAGGTCT ACCTGCCTAA TACAAAAAGA AAAAAAGAA 21300
TTTTAACAAA CAAATGAGGG AATCAGATCC AGAAAGTGAT TCTTATAACT TAGATTACTT 21360
AGAGTAGATC TATAATCTGC TCTAGATCCA CTGCATACAG TGGGCCCTTC TTATCATATT 21420
CCATAAATAG CACTTTTCTC AGCCCAGCTT TTGATGATAG CTGAACAGAC TAACAGTTTG 21480
TCTAACAAAG GCTAGAGAAG GGGATAGCAA ATAATGGCCC ACAGGCTGAA TCCTGCCTGC 21540
TGCTCATTTT TGCAAAGTTT TATTAGAATA CGGTCATTTC CACTCATTTT CACACTGTCA 21600
ATGGCTGCTT TTGCGCTACA GCAGCAGAGC TGGGTGGTTG GGGCAGGGGT CACATGGCTA 21660
ACAAAGACTA AAATACTTAT CATCTGACCT TTTACAGAAA GTTTGCTGAT CCTTGGAGTG 21720
TACAAGTATT CTATATTGTT GATTAAGAAC AGAACACAA GTATTAGAAG TTAGACCAGC 21780
AGGTGGTAAA GCTGATCATC TACTAATATA ATGGAAATTG GGGTCCCAA TCAGGACTCT 21840
TGCTTTGATA GAAGGCCATC TTAACGAGGA GGGAGACACC TGCAGGCAAA GTCAGAATTT 21900
TCTGCAGGAA AAGTTTTGAG TCCATTTCCC CTTGTGAACA AGTGCTCAGC TATGCATTTT 21960
ATCTTTAGTA ACCATGCTTC TATACCTGGT TCTCCTTGGC AAAGATTTCT TTCTTCAGTA 22020
AGTCTCAAGA CTTTCTGGGA AGGTAGGGAG ATATGGGGGT AAAAGTGTC CAGGACTTAC 22080
TGAAGGAAGT GTTTTATGAT TATCTGATAG AATCACTGTA TCATGGTAGA GAAGGCAAAC 22140
AGAATATAAT CTGAAAATAG AGGTGAGGGT GAACAAATGG GCACTAAAAG TGAACTCAGC 22200
ATCAGGAAGG TAGCAAAACA AGACATCAGT CAAAGATATG GGGTGATTCA GACCTAAGGA 22260
AGATTTAATG TGGGATGTTT CCGTGTGCCA GGAGCTGGAC ACTTAAGCAA GAGGAGATCC 22320
AGGAATGTTG CTAAAACCAT GGCCTCCATA CTTTATTGGA ATTAGCACAA CTTATCCTTG 22380
TTTCTTTCAT TTTGCAATCA AAATCTTTAA AAACACATTA TTTAAAAATA CATTATTTTA 22440
AAAGCTAGAA TGAAAATTAT GATATCATTT AGGTGGTTTA AAAACATCC ACCAGCCGGG 22500
CGTGGTGGCT CATGCCTGTA ATCCCAGCAC TTTGGGAGTC CGAGGCGGGC AGATCACGAG 22560
GTCAGGAGAT TGAGACCATC CTGGCTGACA CGGTGAAACC CCGTCTCCAC TAAAAATACA 22620
AAAAATTAAC CGGGCGTGGT GCGGGGTGCC TGTGGTCCCA GCTACTCGGG AGGCTGAGGC 22680
CGGAGAATGG CATGAACCCG GGAGGTGGAG GTTGCAGTGA GCTGAGATCG TGCCACTGCA 22740
CTCCAGCCTG GGTGACAGAG CAAGACTCCA TCTAAAAAAA AAAACAAAA ACCATCCACC 22800
AAAATGGGAA GAAGTGATGA AAAATTACAG TCCAAGAAGA AGGGCCATAG CTGTTTAAAT 22860
CAATTGGTAT ATTTGTTATC TAATATAACC CCACGTAACG ACAGGTATTT AACAAATGTT 22920
TCTGCTGAAT TTGACGATTC CATTTCCCTT ACATCCCAT TGAATCCAT CAGCACCCCA 22980
CATCCAACCC ATCAGTACAT CCTGTGAGCA TTGGCTCCCA AATATAACCT AAATCTAACA 23040
CATATCCTAC TATCTCTGCT GCTACAATT TAGTCTGAAA TCTCATAATC TCCCACTTGT 23100
ACTACTGTAG ATGACTCTGA ATGAGTCTTC TTGCTTCCAT TCCACACAGC ATCCATACTG 23160
ATCTATTTTT TTTTCAATT TTTGTAGAG ACGGGGTCTT GCCATGTTGC CCAGGCTGGT 23220
CTTGAATCC TGGCTTCAAG GGATCCTCCC ACCTCAACCT CCCAAAGTGA TAGGATTTCA 23280
AGTATGAGCC ACTGTGCCTA ACCCTGACTG ATCTTTCTAA GCATAAATCT AATAATGCCC 23340
CTTCCTTGAT TAAACCCTTC AATGAATTCA CATTAGCAA ACAACCTGGC CAGGTGTGAT 23400
GGTTCATGCC TGTAATCTCA GCACTTTGGG AGACCAAGAT GGGAGGATCA CTTGAGGCCA 23460
GGAGCTCAAC ATCAGCTTAG ACAACATGGT GAACTACAT CTCTACAAAA AATACAAGAA 23520
TTAGCTGGGC ATGGTGGTGC ACCTATAGTC CCAGCTACTC GGGCGGCTGA GCTGGGAGGA 23580

FIG. 6.9

TCACCTGAGC CCTGGAGGTC AAGGCAGCAG TGAGCTGTGA TTATGCCACT ACACTTCAGC 23640
CTGGATGAAG TGAGACCTGG TCTCCAAAAA AAAAAAAAAA AAAAAAAGA AGCAGGGCAA 23700
GGTGGCTCAC ACCTGTAATC CCATCACTTT GGGAGGCCAA GGCAGGCCTC CTGGATCATG 23760
AGGTCAAGAG ATCGAGACCA TCCTGGCCAA CATGGTGAAG CCCCATCTCT ACTAAAAATA 23820
CAAAAATTAG CTGGGCATGG TGGCATGCAC CTGTAGTCTC AGGTACTTGG GAGGCTGAGG 23880
CAGGAGAATT GCTTGAACCC GGGAGGCGAA GGTTGCAGTG AGCCAAGATT GCCTGGTGAC 23940
AGAGCGAGCG AGACTCTGTC TCAAAAAAAAAA AAAAAAAG AAAGAAAGAA AGAAAGAAAG 24000
AAAGAAGAAA TCCTTAGTCC TGTCTTAAC ACTTGAGAGG CTGAGGGAGG AGGATCACTT 24060
GAACCTAGGA ATTTGAGGCT CCAGTGAGCT ATGACAGCAC CACGGTGCTC TGGTCTGGAG 24120
AGAGTGAGAC CTTGTCTCTA AAGAAGAGAA AAGAAAAGAA TGAATGAATG AACAAAAAGA 24180
AAGAAGGAAA GGAAAAGAAG AGAGAGAGAG AGAGAGGAAG AAAGGAAGGA AGGAAACAAA 24240
ATAAAATAAA ATAATAATA AATAAACCCA AATCCAACCT CTTTACCCTA ATCAACAAGG 24300
CTCAATAAT CTCATGCCAA CTAAGTCTCT GAACAGCTCC TTCCATTCTA TTGCCAGATT 24360
ACTCCATCTT TCAGCCACAA GACCTTTTTA TCTTCCTTT ACCAGCCAAA CACAATCCTA 24420
CCTCAGAACAA TGTGCACTTT TTCTTTTCTC TGACTTGAAT CTCCTCCACC CATTATATAA 24480
TCTTAGCTCA AAGAGGCTTT TCTTGACAAC TTAGCGAAAG TATTTATCCC AGTCATTCTC 24540
TGCTACATTA TTCCAATTTA TTTTCTCCAT AGTACATTC AGCACATAAA GATTTCCTTA 24600
GTATGTGCTT GTTGCCTTTC CCCAACCTCC TAAATGTCA GCATTCTTG AGGGCAGAGA 24660
CTGTTTCATT CCTGTATCAT CAGCACCTAA GACAGTTCCT GGAACATACC AAGTACTTAA 24720
TAAAAATTTG TTTATTGACT AGCTATGACA CATTTTACTT ATATAATTC ATTTTCTCAG 24780
CAAAATGAAC ACTTTGAAAT GTAATTAATT ACTGATTTTT GCAGTATTTT CTAATTATT 24840
AAATAAAATA TTTACTATTT TGGTCAACCA GAATTCTTAC ATTGTTTTAG CACCCAGATA 24900
GCTTCTAAAA ATGCTTACAA TTAACACAAT TTTATCTAGC AATATGTATT TATCACTAGA 24960
CAGAATGCAC TGAACCTTC TTCATTAATA AAAAGCAATC CAGGCTGGGT GCAGTGGTTC 25020
ACGCCTGTAA TCCTAGCATA GTGGAAGGCC GAGGAGGGAG GATCACTTGA TACCAGGAAT 25080
TCGAGACCAG CCTGGCCAAC ATGGCAAAAC CCCATCTCTA TAAAAAACAC AAAAATTAGC 25140
TGGGTATAAT AGCAGACATC TATAGTCCCA GCTACTCAGG AGGCTGAGAG GTGGGAGGAC 25200
TGCTTGACCC CAGGAGATTG AGGTTGCAGT GAGCCGTGAT TGTGTCACTG CACTCCAGCC 25260
TGGGCTACAG AATGATACCT CATCTAAAAA AAAAAAAAAA TTAGCCAGGC ATGGTGGCAT 25320
GCACCTGTAG TCCCAGCTAC TCAGGAGGCT AAGGTGGGAG GGTCACTTGA GCCTGGAAGG 25380
TAGAGACTGC AGTGAGCCCT GGGTAGCCCG CGCCACTGCA CTCCAGCCCT GAGTGACAGA 25440
GACCCAGTTT CAAAAAACA CAAAAACAG AAAACAAAAC AAACAAACAA AAAAACCCAA 25500
TGCATTGCTG AAATGTAAAA TCCATTATAA AGAAAAGTAC AGGGGTGGGC ATGGTGGTTC 25560
ATGCTTGTA TCCCAGCACT TTGGGAGGCC AAGGTGGGCA GATCACTTAA GGTCAGGAAT 25620
TCAAGAACAG CCTGGCTAAC ACAGTGAAAA ATGCAAAATA CAAAATAAGC CGGGAGTGGT 25680
GGCGCATGCC TGTAATCCCA GCTACTCGGG AGGCTGAGGG GGGAGAATCG CTTGAACCTG 25740
GGAGGTGGAG GTTGCACTCA GCCAAGATCG AACTCCAGCC TGGGTAACAG AGACTCCATC 25800
TCAAAAAAAAAA AAAGTAAAAA GTATATAGTT GATTCTGCAG GGACTTAAAA AAGTATAAAT 25860
ATCTTTTTTA ACATCACAAA GCTCTGATAT CTGCAGGTTT ATGACTAACT ACTAGCTCAC 25920
TCCCATGAAT ACACGTATGT AAACAGGCTC TATACAATCT ACAATCCCAG ACTAAGGGGA 25980
AAAACTGTC CTGTCACTGT GGTCTCCAAC CCTTGGCCCA TTTCTTTCCT CTTGACCACA 26040
AAACTTCTCA GGAGTTGCTT GTTTCCTCTT GATCCACTTA TCTTTAGCCC ACTCCAATCT 26100
GGCATCGGTT CTCAGTACTC TCCACTAAAA CTGCTTTTAT GAAGGCCATC AATGACGTTT 26160
ATGCTGCCAA ATCCAGCAGA CACCTCCTGT TTTCTAATTT TTTTATTGT TATTTTTTAA 26220

FIG. 6.10

GAGACTGGGT CTTGCTCTGT CACCCAGGCT GGAATGCAGT GATGCCATCA TAGCTCACTG 26280
CAGCCTTAAC CTCCCTGAGT TCAAGAGATC CTCTACCTC AGCTGGGACT ACAGGCATGC 26340
ACAGCTATGC CTGGCTAATT ACTCAATCTT TAACATAGCT GATAATTCCC TCCTTGAAAC 26400
ACTCTCAACT TTTAAGAAAC CCTGTTATTT TCCTCCTACA TTTTAGCCA GTTCTTCTAT 26460
CAGCTTCTCC TTATCTGACC TCTAAATGTT AAGAACATTA ACAAAGACTG AACCTAGTTT 26520
TTTTCTCCCC TTAGTGTACT GCTCCTGGGC GATGTCAATC AGTCCCATTG CTTTAGATAC 26580
TATCTGTTGA AACACTGAAA TCACTGGTTT TTTTGT TTTTTTTTTT TTTTTTTTTT 26640
TTGAGATGGA GTTTCGCTCT GTTGCCCAGG CTGGAGTGCA GTGGTGCAAT CTCGGCTCAC 26700
TGCAAGTTCC ACCTCCTGGG CTCAAGCAAT TTTCTGCCT CAGTCTCCCG AGTACTGGGA 26760
TTACAGGTGT GTGCCACCAT ACCCAGCTAA TTTTCTATT TTAGTAGAGA TGGGGTTTCA 26820
CCATGTGTCC AGGCTGGTCT TAACTCCTG ACCTCAGGTG ATCTGCCAC CTTGGCCTCC 26880
CAAAGGTTGG GAAAAGATAT CCCAATCTTT TTCCTATGAT TTCTTAATTG ATCTACTTGA 26940
CATATCCACT TGGACTTTTA ATAGGCATCT CAACTTAAT GTGTTCAAAA TAAACCTCGT 27000
GACTTTCCT CCCAACCTG TCCCTACCTC CCTCAATAAC TAATATTATC ATTCTTATAT 27060
TCATATATTG AATAAATGTT TGTTCCCCCA AGTATTTGTT GCTATAAATT TATGAAGAAT 27120
TCTTTTCTCA CTAGTTATTA TAATTAAAAT GTAATATTTA TTTTCTTTAA AAACCTTTACT 27180
TTGTAGGATT ATTATTTTTT AAACAGGGAC CAACAATAAA TAACTTCTCT ACTTGATTAA 27240
AACTAGGGCT TCCTCTTG TGCTCCCTCAGG ACTATTTCTT TGTAACAAACA ATAGGCTAAA 27300
TCAGTACTGG TGTCAAAGAA ATCATAATCT CACAACCTTA TAAATACAGC ATGTGGCAAG 27360
GGATTTTCCC ATCTTATATA GTAATAAAAT TTTCAGCTGT GCCATGGCTA AAAGTTTACC 27420
ATCAAAGTTG GAATTTTAAA TTAGAGGTAG TCATCTTTCT TTCTTTTAA AGAAATGGAG 27480
TCTCACTATG TTGCCCAGGC TGGAGTGCA GGGCTATTTG CAGGCATGAC CACAGCACGC 27540
TACAGCATCC TGGCCTCAAG CAATTCTCCT GCCTCAGCTT GCCAAGTAGC TGGGACTACA 27600
GGTCCCTGCC ACCACACCCA GCAGAAATAT TTAGCTTTCT GAATTTCTCA AGTGTGTGTA 27660
TGAATGAGAC TAGTGGGGTC CTTAACCAAG ATTCACAGGA TTTTAGTGA TTTATTAAT 27720
AACTTGGATT TGATCTACC AGCATGTTCT TTGAGGTACA GGTATGTCTT TTATATCTCC 27780
TAATATAGTT CATTACAATG CTAAATACTA AGATGTGATG CTCACACACT ACAGAATAGC 27840
CAAGCAAATG AACTACTTAT TCTCATAGGG CTATTATAAT TAACAAATTC TTGTATCACC 27900
CCATCATTAT CAACAACAAC ATGATAGGAT TTCCTTTTAT CTTGAAGAGT CTGGAAAAAG 27960
GGTAACAGAG AGATATTTCT GAGGAACAAA CTGGTAATGA GGGAGCTACT GTGTCCATTA 28020
CAATACTCCT TCTAGAAGCT CAATACATAA TGACTAATCT CTGGAAAAAA GCAAGTGTGA 28080
GAATGGAAGG CTCTTCTTCA AACTATGCAA AATGAATCAA TCAGCAGTGA ACAAATTTAT 28140
GAGCCAAACA AATTCCTACA AAAATTACCA TCATATGCTG TCATGCATGT CTGCCAGTCT 28200
ATTTATCATA TTATTTAAGA AACAAACATT TATTGAAGAT TTATCATGTG CTCAGCACTG 28260
CCAAAGAGGA AATAAAGAGC ATAATATCTA TTCTAGAAA ATAACATTAA CACAAATAGA 28320
AAACAAGAAA CCATAATGTT AAAAATATTA CATAGTAACA CAGAAAGACA ATGTATAATT 28380
ATACATACGC ACTAAAGCAA AGATAACATA ATTTATAAAT TATGAGGTAC AGAATAGTTA 28440
GATTCTGAAA ATTAATAAATA TCAGGAAAAA CTTTCATGAAG ATGAGATCTG GGCTGGATCC 28500
CAAAGGATAG GCAGGTGGAT CATGTAGAAC AGGGGAAAGG AGTTCCTGAT CGGGGATACA 28560
ATATATGTAA AAACCTGGAG ACAGGACTGA GCGTGAAATG TTAATGGGAC AGTAAAGAAA 28620
TCTTCCTCTG CAGCGGGGGA AAAACAGAA TAATGGGAAA CTGCATGGTT AAAAGGTTTG 28680
ATGTTAAGAT AGTGCTTGA CACAAAAGAT CTTAAAGTTG AGTCAAAAGA GTACAATGAA 28740
AGCATTAGAA ATAGAAGATA AAACACAATT AGGCCGGGTG CAGCGGCTCA TGCCTGTAAT 28800
CCCAGCACTT TGGGAGGCCA AGGTGGGTAG ATCACTTGAG GTCAAGAGTT TGAGACCAGC 28860

FIG. 6.11

CTGGCCAACA TGGTGAAACC CCGTCTCTAC TAAAAATACA GAAATTAGCC GTGAATGATG 28920
GCTCGTGCCT GTAGTCCCAG CTATTTGGGA GGCTGAGGCA GGAGACTCGC TTGAATCTGG 28980
GAGGCGGAGG TTGCAGTGAG CCGACATCGC GCCACTGCAC TCCAGCCTGG GTGACAGAGC 29040
AAGCCTCTGT TTAACAAAAA ACGGTAAAAA TAAATAACAT TTAATATTGT TTTCTGATGA 29100
TATATATGGC CTCTAATTGT AAAGCTGAAT GCCTAGTTTA CCACTTTTTT TTTTTTTTTG 29160
AGACGGAGTC TTGCTCTTGT TGCCCAGGCT GGAGGGCAAT GGCACGATCT TGGCTCACCA 29220
CAACCTCTGT CTCCCAGGTT TAAGCGATTG TCCAGCCTCA GCCTCCCGAG TAGCTGGGAT 29280
TACAGGCATG TGCCATCATG CTCAGCTAAT TTTGTATTTT TAGTAGAGAT GGGGTTTCTC 29340
CATGTTGGTC AGGCTGGTCT CAAACTCCCA ACCTCAGGTG ATCCACCCGC CTCAGCCTCC 29400
CAAAGGGCTG GGATTACAGG CGTGAACCAC CGCGCCCGGC CTATCATTCT TATTTTATGC 29460
ATTAGGAAAC TAAGGCTCAA CAAGATTAAG GCTGTCTAGG GTCACAAAGA TTGTAAGTGG 29520
AGGGGCTAGA ATTCAAAATG AGACCTGCTT GACTCCTAAG CCTGTACCAT TTCTACTATA 29580
TTTAGAGTGA AGTAGATGGG TTGAAGAAAT ATTTAGGAGG TGAAATTTCA AAAGTGTACA 29640
GTCAGAAGAG AAGACATATA TGGAAACCTA AATTTTCACA CAGTAAAGTG TCAATAATAA 29700
AGGCATAATG CCAAATGAC AGAGGCTGTG CATGGTGGCT CATGCCTGTA ATCCCAGCAC 29760
TCTGGGAGGC TGAGGCAGGA AGATCACTTG AGCCCAGGAG TTTGACACCA ACCTGGCCAA 29820
CACAGCGAAA CCCCATCTCT ACTAAAAATA CAAAAAATTA GCTGGTAATG GTGGTACACA 29880
CCTGTAATCC CAGCTACTCA GGAGGCTGAG GCATTAGAGT CACTTGAACC TGGGAGGCAG 29940
AGGTTGCCAT GAGCCAAGAT TGTGCCACTG CACTCTAGCC TGGGCAACAG AGTGAGACTC 30000
TGTCTCAAAA AAAAAAAAAG GAAGACTCGA GGGCTAGAAC CCTGAAATTG GGAATGAACA 30060
GGACTGGCTG AAAATGTTTC TTGCACCTGA TAAAAATCTT GAAGAAGAAT GCTTTAAATA 30120
GATAAGAAAG GAGAGAGAGA GGTGGGCGAGT GAGAGGAGAC CACCCTAAGT AATCAGAGAT 30180
TACTTACGTT GGTACTCAG GCTGGTCTCT GAATCTGATT ATAAATGAAA TAGAGATTAC 30240
TTAAACAAA GGGCTGTAAG GTAGCACTGT CCAGCAGCAC TTTCTATGAT GGAAATCTTC 30300
TATATCTGCA CTGTCCAATA AGGTGTAGCT GCTAGCACAT GTGGCCACTG AGTACTTAGA 30360
ATATAGCTAC GACAACCGAG AGGCTGAATT TTAATTTTAA TTTAATGAAT TCAAACAAAT 30420
TTATTTTAA TACAGCACTT TAAATTTTAT TTTTAAATTT TAATCTATTA TTTATTTAGA 30480
GACTGGGTTA TGAGACTGGC TAATTTTGT ATTTTGGTA GAGACGGCGT TTCACCATGT 30540
TGCCCAAGTT AGTCTCAAAC TCCCGGGCTC AAGTGATCCA CCTGCCTTGG CCTCCCCGCA 30600
AAGTGCTGAG AATACAGGTG TGAGTCACCA CGCCCGGCCT AAACCTAAAT TTAAATAGCC 30660
ACGTGCGGGT AGTGGCTACC ATACTGCACA TGCAACTGTA AGATGTAGAA GTCAGATGTG 30720
AGCAAAGAAA TGACAAGCCG TTCAATGCTG TTAGAGAATG AAATTCAAGG TTCCAATGAT 30780
CTGAACCTGT GTCCCCTCAA ATTCGTATGT TGAAATCTTA ATCCTCAATG CAACAGTATT 30840
AAGAATTTGG GGCTTTAGGA GGTAATTTGG TTTTGAGGGT GGAGCCCTCA TGAATAGGAT 30900
GAGCACCTGA GGTAGCCTCT TTGACCCTTC CACCATGTGA GGACACACCA CGAAGGCACC 30960
ATGTTGGAAG CAGAGAGTGA GCACTCCCAA GCACTGAAT CTGCCACATC TTGATTTTGG 31020
GCTTCTCAGC CTACAGAACT GTGAGCAATA AATATCTGCT GTTTATAAAT TATCCAGTGT 31080
AAAGTATTTT GTTATAGCAG CCTGAATAGA CTAAGACAAA GGTGGACTAA GGCAGGATAA 31140
CAGGTTAGAA AAGGAGGCAG GGCCTTTTTT TTTTTTTTTT TTTTTTTGAG ACAAAGCCTC 31200
ACTCTACCC AGGCTGGAGT GCAATGGCAT GATCTTGGCT CACTGCAACC TCCACCTCCA 31260
GGGTCAAGC AATTCTCCTG TCTCAGCCTC CCAAGTAGCT GGGATTACAG GTGTGCACCA 31320
TCACACCCAG CTAATCTTTT GTATTTTATG TAGAGACGGG GTTTCATAT GTTGGCCAGG 31380
CTAGTCTTGA ACTCTTGACC TTAAATGATC CACCCGCCTC GGCCTCCCAA AGTGCTGGGA 31440
TTACAGGTGT GAACCATCGC GCCTGGCCGA GGCACAGTGT TTTTACAGAG AAGCCTGTTT 31500

FIG. 6.12

AAGGTTTAAT CATATAAAAT GTATGATATC CAGTAAGTTT TGATATAAAA AAGAAACACC 31560
TGGCGATTTT ATATAATATA TTGTGCTAAG GAATTTTAAG CACTCTACAT TCTGCTCTCT 31620
AAGCTCTGTA AAGAGCACCA GGGATTTTTT TTTTTTTTTT CTTTTTGAAC AGGGTCTTGC 31680
TCTGTCAGCC AGGCTGGAGT GCAGTGGCAC AATCTTGGCT CACTGCAACC TCTGCCTCTC 31740
GGGCTCAGCG ATTCTCCAC CTCAGCCTCC TGAGTGGTTG GGACCACAGG CGCATGCCAC 31800
TACATCTGGC TAATTTTTTG TAGAGATGGG GTTTTGCCAT GTTGCCAGG CTGGTCTTTA 31860
ACTCCTGGGC TCAAGCGATC CTCCACCTT GGCCTACCAC GCATGCCTGG CCACAACAGG 31920
GATTTTTAAA TGTAAGACTA CCTAGTCAAC TCTTATTCTA TATTAACAAT ATAGACAAGA 31980
AATAACCTCT AAGTAATCTC TATTTCAATT ATAATCAGAT TCAGAGGTTT TCTTATGCTT 32040
TACAATATTG TCCTACTGTG GGTAGCGCAA TAACTAAGGT AATCTGAAAG ACCAGTTATA 32100
TTATATACTA TAGTTAAATG CATTTCAACT GCATGGGAGA AAGCAACTGT GTTCTTTCTT 32160
CTCAATTTTA ACAGAAGGAA AATTGTCAAA ATTAGCTTAT TTAGAATGTC CTATCAGAGA 32220
ATTATTTTGA TTAAATATA TTTTAAATCA ATAAATATT TCTCTTTGGT CAATACTTGT 32280
CAATATAGAA TAATATCTAG CCACAAAATT AAAAAAAAAA CATTTTCCCC TATATTACAT 32340
TCATGGATCT TCTTGAATTT CTGTTATCTA GGTGCTTTTA AAAGTCATAT TTCTGATAAT 32400
ATGAAATCAC AGCTCCTTTT CTTTGGCATA TTAGTTACT GTATTAAGAA AATGTACAAC 32460
ACATAATTTA GAATGGGTAA TTATTATATT CTCTTTATTC TTATTGAA AATGACATGA 32520
AAATTACCAG TCTTCCCAGG TAATATAATT TAAGTTAAAG AACATCTACA TACTACAACC 32580
AATACCCATT CCCCTATGTT ATGTTTGAA AAACATAGAA GTATCTTTAG TAGTACTCTT 32640
AGAAATTATC CCAGGTTTCT CATATTGGTA TTTTATTCC AGGTTTAAAGT TACAGTATTT 32700
TGGGCACCCC AAGTTTAAATA AACTATTCCC TGCAGAAACC TGACAAGTGA AGTTGTGGCT 32760
GGGAATATGT TAGTCTTCTAG ATAAATGAA TTGTTTAAAGA ATTTGCTAAA GATCTCAAAG 32820
CATCTTTCTT AAATCTAAAG AAAGTCAGGA ACAAAGCCAC AACCAGGACC ATAGCATCAG 32880
AAGATGGAAG GTTGCTTTGT CTTCAAATT AAAAAACATT TTCCATTTTA AAATAATTTT 32940
ACTATTTACC TGTGATACTG TTGAAAATTA TGAAAAACA GATAATTTAA AATTTAGTGC 33000
TTTTTTTTTA AAAAAAAAAA AAAGCGAATC CCTGGGACAC TTCATATAGT GCAAAACAAC 33060
AATTCAAGAA TTCAAGCATT GAAAGAAATA ATCTCTTATC CCCCAGTCTC TGAAAGGGAT 33120
TGCCTTTACT ACTGTTCCCA TCTTTATGTC CATATGTACC TAAGGCTTAT CTCCCCTTA 33180
CAAGTGAGAA ACTATTCAGT ATGGCTTAGT CATTTTAAAT GCAAGAGAAT AGGTAAAAAT 33240
GCCAAGCACC AGCCAGAGTT TTTTCTTTGC AGATAGATGT GACTCTTACA GGAGCAGCAG 33300
GGATTTCCCA CTTTGGGCGG AAAGCAGCAT TTAGGTATTC CCCCTCCAGT GCAGTTACAG 33360
ACCACCCCCG CGTAGAAGCT GCTCCTGTCC TCTGTGGCAT GTCAGCCTCT GATTATCTTT 33420
TAATAAACAA TATGGCATAT TAAGTCTCTT TTATGCCCTT CTTTGTATTC CCAGGTACCA 33480
CCTCCATGTC AGGATAACAA GAATTTGGTA ATGTTTGTG AATAAATTTA GCAGAAGTTG 33540
AAAGAAAAAT CCTGTTTCTA CAGAAAGATA CCACTGGCTT TTGGGGAGCC CGAGTTCATG 33600
ATGAAACTAA AGAAAGCCAC AAAAGTTCAC CTCAATGCCA AGACATTTCT TGATTTTTGA 33660
AAACCCAGTT GTCGAACCAC CCATCTATAG AAAGTTGAAA GACTAAAAAC TATCTTACTC 33720
TAAACATTTT CTAGGAAGTT GATTCTACAA CACATTTTGG TTTTCCAATT TGGCTTCTAA 33780
TAATTATTTT AAAGTTTCTG TGGCCTAAAT TTTGTTTAC ATTGATCCTT TGAATGGACT 33840
ACTGTTTCCA CATTTTAGAA CATTTAAAAA GATATCTACA ACCCGAGTCT AATCATAAAA 33900
AAAATCAGAC AGATCCAAAA TGTGGAACAT TCCACTAAAA AAGGAGTGGG GAGAGGTCTT 33960
TATTCTTCCA AAAATATCAA TGCCATAAAA GACAAAGACG GCTATGGAAA TGTTACAGAT 34020
TGAAGGAGAC TAAAGTTAAA TGCAAGAAAG GAAAAAATGG CATATAGGAC AGTATTGAAT 34080
TGACTGACAA AACTGGATTA CAATAGTAGA GTATCAATGT TAACTTGCT GAAGTTGCTA 34140

FIG. 6.13

ACTGTATTTT TTAGGAATTA TTCACCTAAG AATTTAGGCA CACAGATATG ATGTATGTAA 34200
GTTACCCTTA AATGGCTTAG AAAAAAATGT GTGTATATTC ATTTACATAC GTATCTACAC 34260
ACACGTGTAT TAGCGGAAGA GAGCAAGGCA CACATGTGCA TAAGTGATAA AGCAAATGAG 34320
ATGAAATCTT TATTTTTAAA TTTAATTTTG TAAGTTTCAG CTTTTTAAAA TTTTAGATTCT 34380
CGGGGATACA CGTGCAGTTA TTAGTTGGGT ATATTGTGTG AAGCTGAGGT TTGGACCTCT 34440
AATGTTCTCTG TTGCCACAAC AGTGAACACA GTACCCAGCA CGCAGTTTTT CAGCCCTTGC 34500
CCCCCTCCCTC CCGCTCTCCC TCCTTGCTTT TGGAGTTCCC AGTGTCTACT GTTCCCCTCT 34560
TTATGTCCAT GTGTACCCAA GACTTATCTC CCACTTACAA GTGAGAGCAT GCAGTATTTA 34620
GTTTTCTTGT TCTGCGTTAG TTCCGTTAGG ATAATTGCCT CCAGTTACAT TCATGTCACT 34680
GCAAAGGATT TGATTTCACT CTTTTTAATG GCTGTGTAGT ATTCCATGTT GTATAGGTAA 34740
CACATTTTCT TTATCCACTC ATCAATTAAT GGGCACTTAC ATTGATTTCA TGTGTTTGCT 34800
ATTGTGAACG GTGCTGCAAT GAACATCTGA GCGCAGGTGT CTTTCTGGCA GAATGATTTA 34860
TTTTCTGTG GGTATATACC CAGTAATGGG ATTGCTAGCT CAGATAAGTA TTTCTATTTT 34920
TAGTTGCTCT CCACAGGGGT AGAACTAATT TGCATTCCCA CCAACGGCGT GTAAGTGTTT 34980
CCTTTTCTCC ACGGCCTCGC CAACATACGT TCTTTTCTGA TTTTAAATAG TAGCCATTTT 35040
GAACTGGTAA GAGATGGTGT CTCATTGTAG TTTGGCTTTG CATCCAAATG AGACAAAATC 35100
TTAATGACAG GTGAATCTAG GTAAAAGGCA TACAGACGTT CTTTGTGTTG TTTTTTAAAC 35160
TTACATTTGA AGTTATTTT AAATGAAAAA TAAAAGCAAG CAAAAAAGG TCATTCTTCA 35220
TCTAGTAAAC TCTTCAAAGA TTACCACCCC CTTCAACAGT TTTTCTGGT TCTAGTGAGT 35280
CTTCTCCCAT TTGTTTAGAT CTTTGTGAA ATGTAGTCTC AGATAAAAAA TTGTATTTT 35340
ATTTCTTTTA CATATTTCAA ACAATCTAAA TTCTTTTAA ATGAAACTCA TAAAAATAC 35400
TGCATTTGTT TCTAAATAAA ATGGTAGAGG TAATTTGCAC CTTTCCAAAC AGAAGCAATA 35460
GGAGCAACCC AGATGTTCTA GCCACGATCC AAGTCAACCA CATTCAATCT AAGAAGTAAT 35520
TGAAGGCTGT AACGACTTCT GTAAGGCCTA CAAAATGAG TTCAGACACA AGCTCTGCTC 35580
AGTAAAAATC TAGTGGCAGA TGATATATAC AATGATCTGA GAAAAAGGCA GAATCAACAA 35640
AGGTGTATT TTTATCTATT GCTGCGTAGC ATATTTCCCT AACTTTAGTA GCTTGAAACA 35700
ATAAACATTT ATTATTTTCA AAAGTTTCTG TGGTCAGAAA TCCAGGAGCA GCTTAAGTGG 35760
GTGGATCTGG CTCAGCTGTA GACAAGATGT CGGCTGGGAC GGCCATCCTT TGAGGGGCTCT 35820
GAGGGCTTTG AGGGCTGCAC GATCCAATTG CAAGGTGGCT CACTCACATA CTAGGCAAGT 35880
TACTGCTGGG TGCTGGGAGG AGACCTTAGT TTCTTATCAC ATGGACCTCT CCACAGGGCT 35940
GCTGGAATGT CCTCATGACC TTCCCATAG TGAGTATTCC AAGACAGGAA AGTGAAGGCC 36000
ACAATGTCTT TCATGACCTA GCCTCAAAAG TGACATACTG TCATTTACAC AATATTCTAC 36060
TGGCTGTACA AGTTAATCCT ATTTAGTCTG GGAGGGGACT GCATAAGGGC ATGAGTAACA 36120
AGAGGCAAGA ATCCTTGGGG GCCATCTTGG AAGCTGGCTA CACAGAAGAG AAAACACCAG 36180
GGGAGTGCGA AGAAGGTGCA ATTAACTCA ATTCCTTGGT ATGCCAATGG TAAGAAATAT 36240
TAGGTGATCT CTGGGGTGTA ACCTTTTTAA TTAGTTCTT CACTGAATAA TCTGGCCAGT 36300
AATTGTAATA CAAAATACGG CACTCTGACA ATATTCTCTC CTTTATAAT CAATTACACA 36360
CCAGAATATA TATAAGAAA GACTTACAAA GTCACAAGTA ATTGTTTGGT ATTATTTTAA 36420
TAATCACATA CTAGGGCCCT ACAATTAGCA TTCACAAACA TCACTCCATG TTGGCCAGAT 36480
AAGTCTGTCT TTATAGTGGT TTACCATACG CGCCTTAGCA TGAAGTTACA TGTGGTTTCC 36540
TTAGCCATCA GATGCTCCAA ATGCAAAAAA TGTCTCACCA CAGTCACAGA ATCATGGAAT 36600
CCTAAAGTTA CCTGGGGTTT CTGAAAATCT CATGGGAACA ACTCACGAGA ATTAAGGCTT 36660
AAGAAAGTGA TTTATCAAAG AACAAAACCA GCAAGACTTG AGTTTAGAAC TCGCAGCAGA 36720
GTTGTGACTA GAACCTGTTG AAATAGGCAA TGAGAAACC CAGACTAAGG CACATTCTCT 36780

FIG. 6.14

ACAACCTTTAC TATGCAAGTA TGCTTAGATA CTCCTTAGCA AACAGCAGGC CTTGAGTAAA 36840
TTCTTTCAGA ACTGAATACA CAAAGGATAC AGAACGGAAT AACTAACA TAGTGCATGA 36900
TGTGCTCATT TCTGTAATAG AAATGAATTA ATTCTGATCC ATCTATAATT TATTATTGCT 36960
CCATGATTAA CGGAAGGCAT AGGAAAGATG ACTGGAATAG TGTAAGTAGT ACAAACAAGT 37020
ATTACACTTG ACTGAACCTC ATTACACTGC AATTGCATAT TATATAGTAT GTAGGTGAAC 37080
AAATACTGGG TTAGTCAGTG GACCTACATT TGAATACTGG TTCTGCTCCT AGACAGCTGT 37140
ATGATTTGAA TGACTTCTTT ATACTTTCAT AGTTTCTCTG TTCTTCTCTG TAAAACAAAG 37200
GCTTAGAAGA TATTATGGGT TAGATTATGC CCCTTACAAA AGATGCTGAA GTCCTAAACT 37260
ACAATACCTG TGAATGTGAC TTTATTTGGA AATAGGGTCT TTGCAAGTGA TAAAGAAGAG 37320
GTCATGGAGT GACCTAATCC AATACGACCA GTGTCCTTAT AAAAAAAGG AAATTTGGAT 37380
ACAGATACAC ACAAACAAGG AGAATATCAA ATGAACATGA AGGCAGAGAC CGGGGCGGTA 37440
CATCTACAAG CCAAGGGACA CCAAAGATTT TCAGCAAATC ACCAGAAGTT AGGAAGAGTC 37500
ATGGGACAGG TTCTCACAGT CCTCAGAAGA AACCCACCAT GTCAATACAT CATTTTGGAC 37560
TTCTAGTCTT CAGAACCGTA AGAAAATAAA TTTTGTGT TCAAGCTACC CAATTTGTGG 37620
TACTTTGTTA CAGCAGTCCT AGCAAACCTAA TACAAATGAG CTCTTAACAC TGGTCTAAAA 37680
TAGGATAATC CTATGAAATG CTACAAATGT TTGGGAAGAT TTCTCATACT CAACTGTTTA 37740
CAGTATACCA CAAGCCTGTC AGTTGAAGAT ACAAACAGAC CCTCTATAAT CCTCTATACT 37800
TATATGCAAG GAACAGCACA CTTTTCTGC AAAAGGTCAG ATAGTAAACA TTTTAGGCTT 37860
TGTGGGCCAA ACAAGGTTTC TGTTACATTT TTTTTTATA ACTCCTTAAA AATGTAAAAA 37920
TCACCCTCAT CCCAACGGAC TACAGGAACA GACCTCAGGT CACATTTGAC TCATAGCCTG 37980
ACCCCTGGTG TGTAGGGTTA ACAAGCCTCC TTTCCCTGGG CTCCTTTTTC TTTCAGCATT 38040
CCAAGCCAAA GGAAACTATC TTTTCAAAT CATTCTCTCT CCTAGGTGGG ACATCTTACA 38100
CCAGCCCAGG CATGCTTCCG ATAGCCTTAG AGTAGCTGTC CCTCCTCAG AATTACTGTC 38160
TAATTGGCTA GAAGTTAGCA ACTTTTTACA TTTTCCTTC AATTCCTTC CATTAGAAG 38220
AAGGCATGCA CCGGCAAATT ACTTGTGACT ATCAATGACA TACTCTCAGA AGCACCAGTA 38280
CCCCTGTGTT GTTTCTAAAC CCATTCTAAT AGACACATAC CCCAAGGTTA TGCTGTTTGT 38340
CATCTACAA AATGACTTAC ATCTAGAGAT TTAAATAATT AATGTACTTT TCATAACTAC 38400
CAGGTACAGT AGATCTGATA ATGGCAGAGC TAAGCACATA TACAGAAAGT AGGGCAAGGG 38460
CCAGAGACTC ATTTTAAAGC AATGTTACAA GATCGTCACT GTTGCTTTTC ATTTTCTAA 38520
ATGTGGCCAC TGCTGTTTTT TCACTAAAGG AAATGTTTTA TGTAAGTGA ATAACAGTAC 38580
CTGGCATAAA ATAAGTGCTC AATAAATGTT AAGGCCTTCT CTCCCTCTTC AACTGGCCTC 38640
CTCATTTTTC ACAAAGTGAA ATAGAAAAAC AACATGGAAG ATAATCCTGT TGCTTAGGAA 38700
AAATAACTAA AGCTTGCTAG ACAAATACA CCTGAAAATA TAGGAAGTGA GCTATAGCTG 38760
GCCTATATGC ATGTATGTTG GAACAGGACA AGATAGTGTA GGGTGGGGTG AAGAGGACAG 38820
AGAAATGGAA GGAAAGGGGC TACAGCCTTG GTGGCAAAAT AAAGGATAAG ACGACTCTTT 38880
TAAAATGGTC TATTTCAAAT GCTGGGTTGT GAAACTTAAT TTGATTACTT CATGAGAAAC 38940
AGCATCTATA ATCCATCCCT GATTTTCTA CAACAAAAAT TTATTATTTA TTTTATGTTT 39000
GTGTGTAGAT CTTTATATA TATACATGTA CACACGTATA TGTATATATT ATATATGCAT 39060
ATGCATATAT ATGTGTATAT ACATATATAA TATATTGTGT GTGTATGTGT GTGTATATAT 39120
AATTTTTTTA AAGGAATGGG GTCTCACTAT GTTGCCCAGG CTGGACTTGA ACTCCTGGGC 39180
TCAAGCAATC CTCCACCTCA GCCTCCCAAG TAGCAACCAA CAGTTTTAGT TTTGAAAAA 39240
TAACAAATAT TAAACACCCA TGTGTAAGGG TTGGTACTGG GCCCTGTGTT AGTTTGCATG 39300
GGCTGTCGTA ACGTAACACT ACAGGCCGGG CACAACGGCT CACGCCTGTA ATCCCAGTAC 39360
TTTATGAGGC CAAGGTGGGC GGATCACCTG AGGTCAGGAG TTTGAGACCA GTCTGACCAA 39420

FIG. 6.15

CATGGAGAAA CCCCGTCTCT ACTAAAAATA CAAAATTAGC CATGTGTGGT GGCTCATGCC 39480
TGTAATCCCA GCTACTTGGG AGACTGAGGC AGGAGAATCG CTTGAACCTG GGAGGCGGAG 39540
GTTGTGATGA GCTGAGATCA GGCCATTGTA CTCCAGCCTG GGCAACAAGA GCAAAACTCT 39600
GTCTCAAAAA CAAAAAACA AAAACAAAAA AACCCTGATA ACACTACAGA CTGGGTAGCT 39660
GGACCAACAG AAATTTATTT TCTCACAGTT CTGGAGGCTG GAAATCTAAG ATAAAGTTGT 39720
TGGCTGGTTT GGTTTCTGAG GCCTCTCTCC TTAATTGCA GATGGCTGCT TTCTTGAAAT 39780
GTCCTCACAT AGCTGTCCCT CTGTCTGTTT CTGGTGTCTC CCCACGTATC CAAATTCCT 39840
CTTCTTATAA AGATACTAGT CATATTGGAT TAGGGTCCAC CATAAAGACC TCATTTAAAC 39900
TTAATCACCT TTTTACGGCC CTGTGTCCAA ATACAGTCAC ATCCGAGTT CCAGGGGATT 39960
AGGGCTTCAA CCTATGAATT GGGGGTGGGG CACAATTCAG CCCGTAACAG GCCTAGACCT 40020
TAATTTGTCA ACACTACAGT TAGATTTATA GTATAGTAAC TGCATCTGTG CTCATCTAAA 40080
TGTACATCCC AAATGAAATA ATATAGCATG ATGATCTGAA TTTATTAAAG GCAATTTTTC 40140
CTATAGAAAC CCAAATCTAT AAATTATATA CAACTGTGG TAAGTTACTC GATACCTTGC 40200
CAGGACTCAT CTATGGTGGT AGATAGACCA CAAAGAGTAC CACTGAAAGA TCCCTTTCCT 40260
AATCACAGTT TCCTCACTGG CTTGCCACAA AACCTAAAT TCTTCTATTC TTTCATTGGC 40320
AATTTATTTT CCCTGAAAAT GTAAATAATC TCTGGCAGAG CAATCTATTA AGTGATCATC 40380
AGCCACTAAC ACCTTAGGGT AGAACAGCTC AGATCACAGT CTAAAATAA ATTCCATCAG 40440
TATGAAATTT TCTTTATTAC TGCTCCGCTA CTGGAATGTT AGATCACTGT CTGCTTTAAT 40500
AATAATTCTG GTGTAGGTCA TTCAAATTTT GTTTAAGATA ATAAGACAAA TAGCAGGTAT 40560
AAAAACATTC CGTCATCTAA TAAAGCAACC CGAGAACAGT AAGAAGAACG TGATGAAATT 40620
AACATTTTTG AGTACCTGCT AGGAATCAAG TATTCTGCTA GATATTTTAG AAATCATCTC 40680
AATTCATCC TAAAAATTAT TCTGTATAAT AGTATAGGTT GAGTATTCCT AATCCAAAAA 40740
TCTGAAGCTT TTTTTTTCCT GAGACGGAGT TTTGCTCTTG TTGACCAGGC TGGAGTGCAA 40800
TGGCGCAATC CTGACTCACT GCAACCTCCG CCTCCTGGGT TCAAGTGATT AGGGATACTC 40860
AACTGGCTAA ATATAATGCA AATATTTCAA AATCTGAAAA AACCCAAATC TGAAACACTT 40920
CTGGTCCCAA ACATTTTCAAG CAAGGGACAC TCAAGTTGTA TTAATCCCAT TTTACAGAAG 40980
AAGAAACAGG CTCAGATAAA TGAACATCTC AGAGCTTGTT GATAGCAAAG GAGAGATTGA 41040
AACTGTCAGG CCTCTGATCC CAAGCCAAGC CATCACTTCC CCTGTGACTT GCATGTATAC 41100
ATCCAGATGG CCTGAAGTAA CTGAAGATCC ACAAAGAAG TAAAAATAAC CTTAACTAAT 41160
GACATTCTAC CACTGTGATT TGTTTCTGCC CCACCCTCAC TGATCAATGT ACTTTGTAAT 41220
CTCCGCCACC CTTAAGAAGG TTCTTTATAA TTTCCCCAC CCTTAAGAAG GTTCTTTGTA 41280
ATTCTCCCA CCCTTGAGAA TGTAATTTGT GAGATCCACC GCTGCCCGCA AAACATTGCT 41340
CTTAACCTCA CCACCTATCC CAAAACCTAT AAGAAGTAAT GATAATCCAC CACCCTTTGC 41400
TGACTCTCTT TTCTGACTCA GCCCGCCTGC ACCCAGGTGA AATAAATAGC CATGTTGCTC 41460
ACACAAAGCC TGTTTGGTGT CTCTTCACAT GGACACGCAT GAAAGAAACC CTACCTGGTT 41520
CTGTGTCTTA CCTGTTGGGG GCCTGTGGTC AACTACTAG TACGGAGTTT TAGTGTCTC 41580
ACTTTAAAAA TGAGGGTTGT GGCCGGGCGC GGTGGCTCAC GCCTGTAATC CCAGCACTTT 41640
GGGAGGCCGA GCGGGGCGGA TCACGAGGTC AAGAGATCGA GACCATCCCG GCTAAAACGG 41700
TGAAACCCCG TCTCTACTAA AAATACAAAA AAATTAGCCG GCGTAGTGG CGGGCGCCTG 41760
TAGTCCCAGC TACTTGGGAG GCTGAGGCAG GAGAATGGCG TGAACCCGGG AGGCGGAGCT 41820
TGCAGTGAGC CGAGATCCCG CCACTGCACT CCAGCCTGGG CGACAGAGCG AGACTCCGTC 41880
TCAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAATGAGG GTTGTAAGGT 41940
AACTACCTAC TTTTATAGC ATTGTAGTGA AGTTGAAATG AATTAATCCA CATATATTAT 42000
AGTGTGGTAG AATGCAGCAG AACTGATGAT GTATGACTTC TAAGACTAGT CCTTAAGAGA 42060

FIG. 6.16

CCTGCAGTTT TTGCTTTTGC CCTCTTGGAA CACTCCTGTT GCCATGTAA GAAAACTCT 42120
GGGGAGACTA TGAAGGAAGA GAGCATACTC GGGGCAGGGG GGTGAACAGG ACGTGCACAT 42180
GTACGAGCGT ACAAGCCAGG TGACACCAGT ACCACAGCCT CAGACATGTC ACCGGGGATA 42240
CCAGCACCAC AGCCTCAGAC ATGTCACCGG GGACACCAGC ACCACAGCCT CAGACATGTC 42300
ACCGGGGACA CCAGCACCAC GGCCTCAGAC ATGTCACCCA GGGACACCAG CACCAGCACC 42360
ACAGCCTCAG ACATGTCATC GGGGACACCA GCCCATGGT CTCAGACATG TCCCTGAGGC 42420
CCACTTAGAC CCTTCAACCC CAGCCCAGCT GCTAACTGAC TACAGCCACA TGAACAGAAC 42480
CAGGTGAGAC CAGAGGAAAC TTCCAGTCAC CTACCAGATC ATGACAAATA ATAAACGATG 42540
TTTTTTAAAC CACAAAGATT TGGAGCAGCA TTTGTTACAC AAAATTAGAC AACTATTACA 42600
GTTGCGACTAA AAACATGTTT ATTTACAATA CTAAATTAGA AGTGTAAAGAA TGGGAGAAAA 42660
ACTTCATACT TTAAGAGTCA TTTTTCCTC CAAAACTTC CAACTTTGAA AACTGATTTT 42720
TTATAATGCA TAAAAATTAA AATAACCTTA GAATTTATAT GAGTAGCATA GCCAGCTGGC 42780
TTTATTATCT GTTGACTCA ACACTTCAAT AATCACTGAT GTTTTGAAC TCTTCAGATT 42840
TAGAACTCTT GCCCTTGCTT TAGTCTGGT TAAGCTAAAT AATTGTTCTT CCTCAAGAAC 42900
AAATGACCTT ACCTCGTTTT GTTTTCCTT TCTGAGAGAA ACACATTAGC AGTCTCCCAT 42960
CTTGTTTTTC CTTTTCTGT CACCCAGGAC AGAGGGCAGT GGTGTGATCA CAGCTCTGCA 43020
GCACGACTTC CCCAGTTCA GGTGATCCTC CCACCTCAGC CTCCAAGGA GCTGGGACCA 43080
CAGGCACATG CCACCACGTC CAGCTTAATT TTGTATTTT TTGGTAGAGA TCAGGTTTTG 43140
CCTTATTGCC CCAAGCTGAT CTTGAATTCC TGGGCTGAAG CAATCTGCCT GCCCTGGCCT 43200
CTCCAAGTGT TAGGATTACA GGTATAAGCC ACCGTGCAGC CTTATATTTT GTTTTAAATT 43260
TTCCTCTGTA TTTTCTCTC TGGCAAATTG TTTAGGGAGT TTCTTAGTT TATCAGACTA 43320
AATTTCAAGG CTTTCCTTCC AATTTTGACA TGTAACAGT CCCTCATTTT TGCTTATCTA 43380
GTGATTATTC CCAAATCTGT GTTTACAGTC TAGCTGTCTC TCCTGAGATT AAGACTTGTT 43440
TCTCTAACTA CCTGACGGCA GAATCTCCTC TTGGAAGTAT CAAGGAGGCA GTTCAAACT 43500
GAACTGGGCA TTGGCTCCAC TCCTTCTCCT TCTCTTTACT ATTAATACCC TTTCTCTCCT 43560
TCTATATGAC CACACTAAGT CTTATTTAGG CATCGTTTCT TCTGGGAGAC CTTTGTAGAA 43620
TCTCTGAGGT TATGTTAACA TGCTAAGGTT TTCTTGACAT TCTCAGATTG GGTTAGGTGA 43680
ACTTTTAGCA ACTTATCTT TACTAAAAA GTCATCCCTC AGTATCTGTG GGGAATTGGT 43740
TCTAGGACTC CTAAGGATA TCAAAATCTG CATGAGCAGC CCAGGTGAGA CCAGCAGAAG 43800
CACTTTACAG TCACCTACAG GATCATGACA AATAATAAAT CATGTTTAAG CCACAAAGTC 43860
CTTTACATAA AATGGTATAG TATTTGCATA TAACCTACAC ATCTTCCTGT ATCCTTTAAA 43920
TCATCTCTAG TTTATAATAC CTCATACGAT GAAATACTA CGTAAATAGT TGTTATACTG 43980
TATTGTTTAG GGAATAATGA CAAGGAAAAA AGTCCACGCG TGTTCAGAAT AGATGCTTTT 44040
TTTTCTCGTC TAATATTATG GATCCACAGT TGGTTGAATC CACAGATGTG GAATCCATGG 44100
ATACCAAGGA ACGACTGTAT GCATTTTGAC AATTATACTT CTCATCTTAC CATGCATTCA 44160
ACAAACAGAA CATGTAAAGC GGTGATAATG CTGTGATGAA AAATAAAGCA GGGGAAGAGG 44220
CTGCATCCAT CTAGTGGAAG CGATGCCCTT TTCAATCTGC ACAAAGAGAA AAAGCTGCTC 44280
TCCAAGTTGG GGGGTGGGTG GGTGAGGTAT GTAAATTGGT CAGGAAGGGA TCTGTAGGCA 44340
CTTACAGATT TGACGCTAAT GAGATGGGAA GCCACAGGAA GGTGTGAAG AAAAGACAAG 44400
ACATGATCTG ATTCATGTTT TGATCTGATA CACTGGTTGC TAGATGGAGA ATAAGCTGCA 44460
TGGCGGTGAG AGGAAGCAGA AACAATAGGA GGGTAATGCT ATAATCCAGT GGTCCATAAT 44520
CCAATATCCC CCCAAGGAAC AGTTCGGCAA TGTCTGGTGA CATTTCTGGC TGTCACAAC 44580
GTTGGGGCGG AGTGCTACTT GCATCTAGCA GGTAGAAGCT AGGGATGCTA CTAACATCC 44640
TACAATGCAC AAGACAGCCC TTCCCCAAC ATTGCTGGCC CAAAACGTTG ATAGTACCAA 44700

FIG. 6.17

GGCTGAGAAA CTCTGTTATA ATCTGTCCTA GAATGTAGCT TGGATTGAGA TGGCAGTGGT 44760
AAGAGCTGGA GAAGTGCTTA GCTTCCCAAT GTTTTTTGT TTGTTTGT TTGAGACGGA 44820
GTCTCGCTCT GTCGCCCCGG CTGGAGTGCA GTGGCGTGAT CTCGGCTCAC TGCAAGCTCT 44880
GCCTCTGGG TTCACGCCAT TCTCCACCT CAGCCTCCCG AGTAGCTGGG ACTACGGGCG 44940
CGTGCCACCA CACCCAGCTA ATTTTTTGT ATTTTATAGTA CAGACAGGGT TTCACCATGT 45000
TAGCCAGGAT GGTCTCCATC TCCTGATCCC GTGATCCACC CACCTCGGCC TCCCAAAGTG 45060
CTGGGATTGC AGGCGTGAGC CACCGCGCCC GGCCTGAATG TTTTAAAGT ACTGGTGACC 45120
ATATTCGCTG AGGGATTAAA TGTAAGGTAT GAGGGGAAAA TAGGAATCAG ACACCAGGGT 45180
TACTGCCTG AGCAATGAGA AGAACGACGT TCCTCATACG GAGATGAGGA AGAATGTGGA 45240
ATAGCAGGTA AATAGCATGT GCTTGCTTTG TTTGGGGCTG TGCAGAAGAG ACTGATGGGA 45300
CCAACGTGCT CAGTTCTGGA TATATTAAAC TTGAATGCC TATTTGGCAC CAAGTGAATG 45360
TATCAGGTAG GCAGATGGAT AAATGAGTCT GAAGTTCAGG GGAGAGGCTG GGGTGGCAAT 45420
ATGAACTTGG GAGTCTCCAC ATCTGAATAG TATTTAAAGC TATACAACAG GATAAGGTGA 45480
TTTAGGAACT AAACACAAAT TGAGACGAGA TCCGAGCCCA GAGGCACTCC GATGTTTAAA 45540
AAAGAGGAGG AACCATCAAA AGATACTAAG GAGAAGCCAA GAAGTAGGAG AACTGAGAGT 45600
CTGAGAGAAT CATTATACTC ATTTGATCGA CTGCAACAAA TGCTGCTTAG AGGTCAAGCA 45660
AAATGAGGAC TAAGCAAGGA CCACCAGGTC TGGCAACATG GAGGCCAATG CCGACGTGGA 45720
AATGAGAGTT TTGGTGGGAA GACAGGAATA AAAGTCTCAC AGGTCTGAAT TCAAGAGAGA 45780
GAACAGCAGA AGAAGGGTAG AGGTGGTAGC CATAAACAAT GATACATTCT CTTGAGGCCT 45840
TTTCTTGCAA AGCTCAGTGA AGAAACATGG TTCCAGAGAG GGATTTTTTT TTCTCTCATT 45900
TTACATATGC AAACATATAA AAAAGCTGAA AGAATTGTTT GACAACCACC CTTATTCTTA 45960
CCACAGATTG AACATTTAAT GCCATATGTT TTCCCTGTAT GTACTGTGTA TTGTTTGAGG 46020
ATAACTTCCC CTCTAAATAT ACCTCGGATG TATCTCCTAA AATAAGTCCA TTCTCCTACA 46080
TAGCCATAGT AACCATGAAC ACACCTAGGA AAATTAAGAAA TATATTCTCA AATATATTAT 46140
ATAGCTGGGT ATATTACAAT TTCCCAATA TGTGATTGTC AAACCAGGAT CAAGTCAAA 46200
TCCATGCACA GCATTTGGTT GTCATGTGTC TTTGGTCTCT ATTAATAATG ATGACTGTTT 46260
GAAAAGACCT GTCCTATAGA ATAAATTTGA CTGATTATGT CATGCCATTG AACTTGTTTT 46320
TCTATTCTAG AAGGATAGTT TTTTAGGGTA GTGAATACAT TTATTACTCT TGGCACAATA 46380
GTCTAACATT TCCCAATTTT CTTATATCTC TGCCCTTTCA TTTTCAGAAA ATCAATTATT 46440
CCAAGATTG TTTTTCATTT ATCATCACTT ATTAGCTCTG AAGACTCAAC TGAGCAACTT 46500
TCAGGGTTTA TATACCCTAT ATTCAGAAAA AACTACTAC CATCTCTCAT TTACCCTAAG 46560
AATTCATAGG AGAGCATGTC TTAAAGCTGA TCAATAACCA AACCAAACAT TTTATTGATC 46620
ATATTACATT TGGAAAGCAA AATGAATTTT CTAAATTTT TTCCCTGATT AGCAAAATAG 46680
TGCCCTCGAA CACTTGAGGG TGAAAGTTGT TGTCAAATAT GCCTACATGA CTGGAAATTA 46740
TGACATCCAA ATGAGTTCAC TGGGTCTGAT AATAATATGC TCTACATGCT TATGTCTATG 46800
TAATAAACAG CTTACATCTG GATGAGAAAA TTGATTATAC AAATATTTGG GCTTCTACAA 46860
CTGGTCACTC ATCTGTAAGT ACTTAAAGCA ACTTAAATG CAAACTGACC TAACAATGCT 46920
TATGGTTAGA ATTCCAAAGA ATGTTTAGGC ATTGTCAGGT TATGTTAAAA CATCTTCTGC 46980
CACAATCTTC AAGTGATTTA TCTTTTCTGT TGTGTTGAAT AGCTATAGAA GACAAATGAA 47040
TTCTGCACTC CTGAATTCAA TGAACATTTC AAGTTTCCTC ACTTACACTG TAAGATTACG 47100
TAGCATATTT TAAGAAATAA ATTATAATCA TTTTATTCA CTTATTGAAC TTCTTTTAAG 47160
CTTTGGCATT AGAATTTTAA TCAAAGCACT GCCACTTGCT TACAGTGATG GTTTTTAGGC 47220
TCTTTGGGCC TATGGACTAT TTCAATGACC TTCACTAGCC ATCTAGTCCA CCTTATCCTA 47280
ATTATTACCA CTGCAAAAGA AACCTCACT TGAATAAATC AGTAGATGGG CATGAGGCAC 47340

FIG. 6.18

CTCCCAGGAG ACTATAATTA TTAAC TCATA CTAAAATCAA AATTGTAGCT ATTATCACTC 47400
ATATGGTTTG GCTCTGTGTC TCCACCCAAA TCTCATCTTG AATTGTAATC CCCACGTGTC 47460
AAAGGAGAAG CCTGGTGCGA AAGGACTGGA TCATGGGGGC GGCCTTCCCC CTTGCTGTTC 47520
TTGTGAAAGA GTTCTCCGAT GGTTTAAACG CATGGGACTT CCTCCTACTT GCTCGCTCTC 47580
TTCTGCCACC ATGTAAGATG TGCCTTGCTT CCCCTTTGCC TTCTGCCATG ATTTTAAGTT 47640
TCCTGAGGCC TCCCAGCCA TGCAGAAATG TGAGTCAATT AAACCTCTTT TCTTTGTAAA 47700
TTACCCAGTC TCAGGTAGTT CTTTACAGCA GTGTGAAAAT AGACTAATAC AATCACCTTA 47760
TGGTAAGTCT GTCTATAAAT CACCTGAATC TTCACAGACT ATCTAGAAGA ACATGTAACC 47820
AGAGTAGTTC TTGATCATGC TATATAAATT ACTGATACAG AAATAGAGCT AGACAGGAAG 47880
GGGCTGGTAG TAGAGAATCA TCCTCTGGAC ATATTCTCAC AGCCTAATCT CTAGCTAGCA 47940
AATTTTATAA TATATATAAA AATACAATTA TTTACAAAA TTACCATGAA ACGATTTTAT 48000
TGGGATATTA GACATTACTG AATTACTTGT TCTGTGAGGT ATACAGTGAA ATTAACATGT 48060
TATAAAATTG TGGTAGCCGG CCCCCAAGAT GGCCTCCAAT GAATCCTTCA CCTCTTGTA 48120
TTCATACCTT TGTGTAGGTA GGTCTGTGTA ACCCATAGAA TACAGCACAG TGACAGTAGG 48180
TCACTTCCGA GGTTAGGTTG TGAAAGACAC TGTGGTTTCT GCCTCTCTCT CAGATCACGT 48240
GCTCTGGGGG AAAAGCCAGG TGTCATTTTG TGAAGACACT CAAGCAGCCT TTAGATGACT 48300
GCAACCACAT AAGAGGCTCC GAACTGGAGC CACTCAGCTA AACCCTCCC AGATTCTCTGA 48360
CCATGTATCA TTTCATACAC AATGTATGAA ATGACAAATG TCTGTTGTTT TAAGCTGTTT 48420
GGGGAATAAT TTGTTACATA ACAAATATA ACTAATACAA TAATACATAC TGATTTAACT 48480
GAAGTTGTAA CTTCATAACT TATTTAGGTA CTAAAAATCA CAGCAACCCG ATGCAAAGTA 48540
CTAAAAAAA AATCCATTAA TACCTATTGA GACTGTTGA GGGCATGAGG AAAGCTCTTT 48600
CATACTCCAC ATAAAACTTC CTTACCGTAA TATTCATGGC TGACCTCTAC TCTTAACTCC 48660
TTTCTAGGAT AGGAGGGGCT AACTGATCTG ACAGCAAGTT TGGGAGAAAA AATTCTGAGG 48720
CTCGGCCAAC TTCCTCTCTT CTTTCCATTT GGGATTTGGC TGAAGTGAAGA GGGTCATTTG 48780
TTTTGGCTG CTCTCTTACA CAGTAAATGT AGTGGGACAA GCTCTATTCT TGTTGATAGA 48840
AAAACTCGAA TTTTAAATCT GCCTAGTTCT TTGCAGCTCG TTGTTGCTCC AAATCTCAGC 48900
TACCTTTTGA AACAACTTTT TTCAGTAAAC TTAATTTCAA TCTTCATGTG ATTTAACTGG 48960
ATCCAAACAC AGGCAGATAA AAAAGGTGGG GCATTACTTA TCAACCTCTA AACTAAGTTT 49020
AATTTTGTGC CCTCATGGAG TTTATAGTAT ATTTGAGGTT TAAACTAAAA CACCTGGTTT 49080
TAAACAGAAA CTATAAAAAA CACGATTAAT AGGTGAGGCC GGGCGCGGCG GCTCACGCCT 49140
GTAATCCCAG CACTTGGGGA GGCCAAGGCG GGTGGATCAC GAGGTCAGGA GATCAAGACC 49200
ATCCTGGCTA ACACGGTGTG AAACCCCGTC TCTACTAAAA ATACAAAAAA TTAGCCCGGC 49260
GTAGTGGTGG GAGCCTGTAG TCCCAGCTAC TCAGGACGCT GAGGCAGGAG AATGGCGTGA 49320
ACCCGGAAGG CGGAGCTTGC AGTGAGCCAT TCGGCCACTG CACTCCAGCC TGGGTGACAG 49380
AGCCAGACTC CGTCTCAAAA AAACAAACAA ACAAAAAACA AATAGGTGAA AGGCCGTGAT 49440
CATTGGTAAG CGTAAGAAAA TCTGAGGGAG AAAAAAATAT AGATGCCAG GCCCATGCC 49500
AAACTCATGG AATCATGCAT GAAACCCAAG CAGCTGCAGT TTTAACAAGT TCCCAATATA 49560
TAGTTGACCC CTGAACAATG CAGGTTTGAA CTGCCTGGGT CCACTTATAA AATGGATTTG 49620
ATTTTTTCA ATAAAAGTTA CACCGAGTGT GCCTGCCTCT CCTCCCTCCC TCCCTACATG 49680
CTCCTGCTCT TAAGCCTCTG CCATGAGGCT TAAGACAGCA AGAACAACCC GTCCTGTTTA 49740
TTTCAATAGT TTTGGGGGGT GCAGGTGGTT TTTGGTTACA TGGATAAGTT CTTTAGTGGT 49800
GATTTCTGAG ATTTTAGTGC AACTGTCACC TGAGCAGTGT AACTGTATC CAACATGTAG 49860
TCTTTTAACC CCCATCCAAC CTTCTTCCCC AACCCGAATC CCCAAAGTCC ACTGTATGAT 49920
TCTTATGCCT CTGTGTTTTT ATAGCTTAGC TCCCACTTTT AAGTGAGAAC ATACCATTTT 49980

FIG. 6.19

TGGTTTCCCA TTCCTGAGCT ACTTCACTTA GAATACTGGC CTCCAGCTCC ATCCAAATTG 50040
CTGCAAAAGA TATTATTTTCG TTCCTTTGTA TGGATGAATA GTATTCCACG ATGTACATAA 50100
ACATTTTCTT TATCCACTCA GCTCCTCTTC AGTCTACTCA ATGTGAAGGT GACAAGGACG 50160
AAGATCTTTA TGATGATCCA TTTCCACTTA ATGATTAGTA AATATACTTA CTTTTCTT 50220
TGATTTTCTT AGTAACTTTT TTTCTCTAAC TTACTTTATT GTAAGAATAC AGTATATAAC 50280
ACATATGACA TACAAAATAC GTTAGTCAAC AATATATGCT ATCAGTAAAC TTCCAGTCAT 50340
CAGTGGGCTA TTAGCAGCTA CGTTTTTTGG GCAGTCAAAA GCATGGGGAA GGAGAGGGTG 50400
GTCCCTAACC CCTGTGTTGC TCAAGGGTCA ATTGTAATAA TACCCATTTA AGAATCCATG 50460
GTATATATGG TAAGTGCAAC AACTCTAGAA GAGAGTGCTA GGAGTTGGAA AAGGAAAGAG 50520
AAAACAGAAT TTAAGCAAT CTGTAAGGA CATGCAGGGT TTAGATGAGG TGGAAGGGTG 50580
AGGGAAAACC AACATCTGCT GTGAGGGCAT ATTAAGTCC AGACATTGTT CTATGTCTTA 50640
CCTCATTTAA GAGAATTTCA TTTACACAT GGAAAACTG AAGCCCAGAG AGGTAAATA 50700
ATTTGCCTGA GGCCAAAATT AGTTAAATA CAGAAGTGGG ATTAGTAGAT GTTTTCATTT 50760
TATCAGTGAA ACTGAGCCTC AGGGAGGTTA AATATTTGT ATGAAGTAAC AAACTGAGA 50820
TTAATATATG GCCAAGTTA AATGAGATCT GTAAATCTAA TGCCTACACT AAAACAAAAA 50880
AAAAAAGTG GGAAGAAAAG GTCTATATTG CTTAGCAAAA CAGAGGTAGG GAAGCAAAAA 50940
TAAACTTACA AAATCAGATT AGACCACCAA AAAACAGTCC CCATTTTAAC TTATGTGGTG 51000
AGAACCATAT ATTAAGACC ACCAGTGGCT TAAAATCTT TTTAAAAAT GAATCTGTTT 51060
TCATTATTCA TTAGTTTTTA TCTAATGAAT AATGTATCTT AACTGATACA TTTACTAAAC 51120
AATTACCAGC TCCAATTAGC ACTCAGTTAC AATTCAATCA TTAACTGAC CCTCAATTTA 51180
GCTGTCAACC TAGTCAAAAC AGTTAAGTGA TTTTACGGTC ATCCTCAGTT GCAGAAGTAT 51240
AATGTTTATG GCTGGAGTCA TTTTATTTT AACTAACATT TTTTAAAAAG ATTGCTTTGT 51300
AACAATGTGT TATGAGTCCT TTGTGGTAAA TACTGCTTTT TTTTGAGAC GCAGTCTCGC 51360
TTTATTGCCC AGGCTGGAGT GCAGTGGTGC GATCTTGGAT CTGAGGCTCC TGCCTCAGCC 51420
TCCTGAGTAG CTGGGACTAC AGGCATGCGC CAACGTGCCC AGCTAATTTT TTGTTTTTTT 51480
AGTAGAGATG GGGTTTCACC ATGCTGGCCA GGCTGGTCTC GAACTCCTGA CCTCGTGATC 51540
TGCCACCTC GGCCTTCCAA AGTGCTGGGA TTACAGCTAT TTTAAGGACT TTTTAAAAAG 51600
TGAAGCTAAA CATTTATTCA TCCCTATTCC TCATCTATAG GGACTTGTGC TCTATTTTC 51660
TTTGAAGACT GAAGTAAAAA TTCACCTTTG TGAGGGTCTT CCTATAATTA AAATTAATCA 51720
TTTTTCTC CATAGCTTCT ACAAACATT GCCTGTACAA CTCTATTTAG CACTTATTTT 51780
ATCCCGCTT GTATGAAAAC TATTTGTTA CAAACGTTT TACTTCTCT TAGGAATAAG 51840
GACTATGCAT TATCACTGT TGTATTCTCC CTGCATTTAT GGCAGTCCTT TGCACATTAA 51900
ATACAAGCTT TTTGGCTCTG TGCATCTCT CATCTGGCTG TTCATCTGTA CCCTTTAAAA 51960
CATCCTTTAT TAAAAAACA GTAAATGTAA AAAAAAAAAA AAGCCATTGA TGAAAAAGTT 52020
AATAGCTTTC TCAATAAGAA AAGAGTATCA ATTATGCATA CGTCTGAAC ACAAACATG 52080
AATGAAATAG GCTATTTAAT ACATTCTGTT TTAAGTAG GTTTGGTCAG CCATGTAAAT 52140
TGAAATTGG GAGCCACCAA GATAACTCAT CAACAAATAT GCACTATGTA CTAGGCACTA 52200
TATAGATGAT GGTGAACCAA ACAGATGTAA TCCTTGCTCT TACAGATCTC ACAACCTACT 52260
ATGGGGCCAA AAATATATGT GTATGTGTGT GTGTTATACA TATATACACA CACATACATG 52320
TATATATACA TATACACATA CACATATATA CATACGCACA CATACACATA TATACACACA 52380
CATACATATG CTATGAGGAA AACAAACAGG TGGTGAGAAA GAATTAGAGT AGGGGTAGAG 52440
GACAGAGGGC TCCTCAAATA GGGTGGACAG CTTGACACAA GACACTCGAG CTAAGACTCC 52500
AAGGATGAGA AGACAGTTAT GTAAAGAAAA GGGGACTAGC ATTGTCAGCA GGTAGCTAAG 52560
GCCTTAAAGC AGACAGTCAT GTGCTGCAAT GCCAGCTTCA AGCGAATACA GTTACTAAAG 52620

FIG. 6.20

CATATCTAAC CTTCTATGTG AATGTAGTTA CTAAAGCATA TCCTCCAAC TCCATTTTT 52680
CTTTTGCTAT TGTTTCTACC ACTTCTCCTT TTCTGTTGAC AATTATTTTA AATTCCTGG 52740
CTAAATTA AAA TGATGGCATG AACTCTGGGG AAAGTAAGAC TACCTATGTC CAAATAATCC 52800
TAAATTCCTT CTAGTCCTTA TGA CTGATCA ATTCACCCTG AAGTGACAAC TATGTCCCAA 52860
TTAGGAAAGA GTGTTTCTT ATCTGCACTT AATTTTTTGA TTTGGAGGCT TCCTGATTGC 52920
TAATCAACAT GTTGTGTGAT TACTTCAACA AGTACTTATA GAACGTTATT TTGTCACTGG 52980
AAAAACGTTT TGCTGCTTTC TGAACCTTAG GTTGCTCTAG AGTCTAGGAA GAGTGA CTGT 53040
ACCTAAAGCA GTTCCTAATT ACTGGACATT CTCAGATCTG CTAGAGCTAC ATGTCCAATT 53100
ACGAGAATAT ACTGGAAAAA GCCCTGGATT AGAAATGAGA GGATGTAGGT TTAGTACCA 53160
GGTCAGCCAC CTTGTTAATG CAAATTTGAG TAAATTGTTA CTTCTTTTAG GCCTTGTTTT 53220
TGCTGTTTTG TTTTCTGAC AGTATGGTCT CTGTGGTCCA GGCTGGAGTG CAGAGGCACA 53280
ATATCAGGTC CCTGCAGTCT CTACCTCCCA GGATCAAGCC ATTTTCATGC CTCATCCTCC 53340
TGAGTAGCTG GGATTACAGG CATGTGCCAC CACACCCTCG AACTCCTGAC CTCAAGTGAT 53400
CTGCTTGCTT CAGCCTCCCA AAGTGCTGGG ATTAGAGGTG TGAGCCACTG TGCCTAGCCT 53460
TACACATTGT TTTCTTACTG GTAAAGTGGG AATATCTAGA AGTTGCATGC TACATAAATT 53520
CAACCATATA TTATTGGCAA AAAATTTTAA AGAAAAACAT CAGCTTAAGA GTACTAATTG 53580
AGTACATGCC TTGGAATGAG CATGAGCTGG AAAGAACAAA CCTGTTGTTA CATCACTCAT 53640
TGCTGTTTTT ATATGCTGCT CATTGTAAAT CTGCTCAGT GGCATGATTT TAGTGTTTAA 53700
AGATTTATTT GTTTGTTTGT TTAGGACAAA GTCTCTACAC ATAATCTACT TGCTTCATAT 53760
ATACATACTT ATGCATATTA TGTATGTACA TACATGCTCT CAGGGCTCAC ATGAAAAAAC 53820
AGCCATTGAG GTGATGTGAT TTATCTCATA TGCTTACTTT AGAGTCAACA GGGTGTGAC 53880
TCCACTATAC AATACTGGCA TGGAGAACAC ATAAGTCAAA GTAGACAGGA CCCAGCCGTA 53940
CCATTGGCTA GGGCACA AAT ATATTCACAT ATGTGGAGAA TGATGTACGT AGAAAGGTCT 54000
TCATTGCACA ATGCTCTTTA ATAAAGATCT GGAAAAAAA AACACCTAAA TGTTCAAAAG 54060
GATAGGGTAG ATGAAATAAT GGTACATTAT AAAATGGAAG ATTATGCAGC CATAAAAATA 54120
AGGAAATACC TTAAATAATA ACAGAACAAC TTTTAAGGTA AGTGAACAAA TAAGGTACAT 54180
AATCACTATG CATAGTATGT ACCATTTACA TAGAAAAAGG GAAGAAAAAT AAAATATATA 54240
TAGTAATTTA TTTGTTCTTA CATGTGTAAT ATTTTCTGA AAAATATACC AGAACTGGT 54300
AGCACTGGTT GCTTCCTAGG CAGAAATGA CTGAGTATCC TTTTGTACCT TTTGAATTTT 54360
GAACCACGTG AATGAATGTG TTACCTATGA ACAAATGAC AAGTTTAGAT CAGCAAGACA 54420
GCAGTTTGAG ATGAAATGGG ATTACACCCT TAGTAGGAAA AACTTTTTTA AGCAGGTGGT 54480
ACTTCTAAGA GCAAATACCT GCACATGGAA TGTGAAACT ATAAGGAACT CTCCTTAAGA 54540
GATCCATCTA TTCCAACTT CTCAATTTAT AGATCTGTAA ACTGAGACCT TAAAAATTCA 54600
GTGACTTGCA TAAGGTCACA CAGCAGAAGA GATGGGATTA GATGCTAGAT ATTTCAATAT 54660
CAAGTTTGA CTATTAAAA TTCAGTGA CTGTGTAAGGT CACACAGCAG AAGAGATGGG 54720
ATTAGATGTC AGATATTCCA GTATCAACTT TAGACTATTA TCACACCATC TTCTCATTTT 54780
CTGGGGGCAA AACAGAACCA AGTAAGTTTG GGCTACATTA CGAGTTGTCA TGTTTTTGT 54840
TTTGTTTTTT TGAGATGGAG TCTTGCTCTG TCGCTCAGGC TGGAGTGCAG TGGTGTAAATC 54900
TCAGCTCATT GCAATCTCTG ACCCCCGGGG TTCAAGCAAT TCTCCCTGCC TTAGCCTCCC 54960
GAGTAGCTGG GTTTACAGGC GCCTCCACC GCGCCCGGTT AATTTTTGTA TTTTTTTTTT 55020
TTTTTTTTTAG TAGAGACGGG GTTTCACCAT CTGGCCAGG CTGGTCTTGA ACTCCTGACC 55080
TCGTGATCCA CCCACCTCAG CCTCCCAAAG TGCTGGGATT ACAGGTGTGA GCCACCACGC 55140
CCGGCCGAGT TGTCATGTTT TATCTAAATT TTAGAGTCTA ATGTATAAAT TAACCTTAAG 55200
CCCTGAAACT ACTAATTTCT TGTTTGGATC ACTATACGGC TACACTTAAA AATATGCTGT 55260

FIG. 6.21

GCATACCTCT ATCATTGCAT GTATACAATA TGATAGATGC ATGATATGAC AGACACACAA 55320
TATGATACAC GTATTTTTTT CTATCCTAAC ACATCTGAAT TTAAGTAAAT AACTAAAATG 55380
TCTTAAGTTA CTTTTTTAAA TATACACATG CATAGCACAA GCGTGTGCCC AAAAATATGA 55440
ATACAGGTTT ACAATTCCTT AACTAAAACC CAAGGGTTGG ATGTGTTTTA GAAATAAGAA 55500
TTTCATACAA TTTTAAAGTG TTACAGGGTA TATAAACCAT TATATAACAC ATACCAGGGG 55560
CCAAGGGCAG CACCCCATAA TCAAACATAT TAATATAGTT TCAGCAAAAC ACATGGGATA 55620
AAGACTATAT ACAGCTTCTC AATAGTTCAG GTCATATTTT GCTACCAAAT GAATTTTGT 55680
GCCAAGCTTA AGAAGTTTTT GGTTTTCACC GCTTTCTGAA TGTTAGATTG AGATGTGGGA 55740
TTACAGACTG TACTCATAGA GTGCTTCTAG AAAGCAGTCA GTCACCTCAA CTCTCATTTT 55800
TTTTTTATGA GACTAAAAAA GAAATCATAG CAAGTAGCTT TTATATCCCA GGTTTGGGCC 55860
AAAGACTTGT ATTGTGGTTA AGGAATCTAA CTTAGTAGAA GGTGCACGAG CTGACATCGT 55920
GAGTGGCTAA AATGAGAGAA AAAAAGAGAA AATCCTAATC ATACAGAAGC ACTGAACTAC 55980
TGCAGCTGTT CGTTAGTTAT TAATTTAATA AAAGCTTCCT CCCTTTAAAT CATGTGAGTT 56040
TATAACTGGA AATAGGTCAA TAAAATTTCT GTCCCACT GCTGACAAGC GATGGACGCA 56100
ATTAGCTTTA ATCCCACTGG AAGGTACTGC ACTCTCTCTG GGACCAGGAT ATGTAGAAAA 56160
AAGCATTTCA AATATATAGG AATAACCAGA AATGTATACA GTATTCTCAA CTTGGGACCG 56220
TTACTCTATA ATATAAACGA AAGGGGTTTT CTAGTCAATC TCTGCTGATC TCTGTACCA 56280
AAGTTCTTCC CTTTATAAGT CTTGTACTAC CTTTACAAG AGGAAAAAGC TCTAGAGCGA 56340
AAACACAGAA CACACTAAAA TCCCTTCCTT TCTCTTACA ACTCAAGCCC CGCCTCCATT 56400
TTGTTTCTGT TACTAATTTT TCTTCTGAAA AAATACCAA TTTACACTGA AAGACTAAAA 56460
TTCAACTTTG CAGACAACGT TTTAAAAAAT ACAATTCAGT TTGGTGATGT TGTTTTGCAG 56520
TCTTACAATT TTAGCTACAT TTTAACTGAA CCAATTGTTT TGTTCAATTT ATGAGTTAAT 56580
ACTCAGCAAG TTTGTTTTTT ACAAAATAGT TATTCCATTC TAAAAATGGA AGTAGCAGTG 56640
GTGAACAAGA AAACAACCCT CTGAGTTTTG TCTATTTTCA GAGGAAGTAC TACTTTCTCC 56700
AATTTTAATC ACAATTCATA AAAAAGAAAA ACCTAACTAG CTAGATCTTA AATATACAAA 56760
TACATTAACA ATCTAGTAAA GCAACAGAAA AAGGTAAACA AACTAACCAG CCTATTTTTG 56820
TCTGGAGAAA CCCCAACAAA CTGCTGGATT CCTTGGCCAT TTGCATTGAG AAGTACCAA 56880
AACTAAAATC CTTTTTACTA AATAATTTCT TCTACACGAG ACTTGTTTCC TCCACACCAC 56940
CCTATCCAAA TTGTCAGCAT TATTCCAGAA TATAATCATT TAGTTTGAGA CCACTAAAAA 57000
ACCCCGCAGT CAAAATACC AATTGTGGTT TTTCTGTAAA GAAATGGTCA GAACTACAA 57060
ATTGTTATCC TAGGACACAG AACCAATCGA CAAAAGGAC TTCTGGAATA TGCTGCCCCC 57120
AAGATTTAGA ATGCACAGGC AGAAATAGCA TACGCGGTCA CGATGTCCCT TAAGCCACAT 57180
GACCTTCCTA CGAAAGCAA GGCTTAACT TATCAATGA GAACTCCCCC TTTCTCTGAA 57240
GTAAAACAA GGCAGGGCAG CTGGAATTAG AGCAGCAGGG ACAGATCGGC TGTTGACTAG 57300
TCAGAACGGG TCGTGGAATG CAAAGTCCCT GCGCTTTCGC TGCTCCCTT ACCGTGAGAA 57360
GATCTGGGAG GGAGGAAAGG AGGAGAAACA CCCAGAATC CTGGTAGAAA AGCCCTGGC 57420
CTCGAAGATG GGCTCTAGGG AGACAGGGAG GGGCAGCTCC GTGTGTGATG ACCCTTTGTG 57480
AACATGCACT CTGTGGCAGC TTCAGCTCCA CCGAGGCTTT GGGAGAGCGG ACTACGGATG 57540
CCCGGCGCGG CCCAGCTGTG AAGGCCGCGC CGGCGGAGAG GGTCCATGGC ACCCCCGCCG 57600
GCTTCGGAAG CCCTTCCTC TCCACCTCC GCGGGTCACC CCAGGAACCA GCGGCTCCCG 57660
ACCACGCTCG CGCGGACCAC GGAACAGCGA CGCGCAAGCA GGTCTCTTC GTCAGCGTAA 57720
TCCCTCCGCA GAAAGCCGCG CACTAGTTTT AATCACGCCC CACCCCTGG CCGCTGGCGC 57780
CACCTCCGCC ACTCGGGCGC TTTCCAGCAG CTTCCAGAAA CGTCGCCTCC CAAACCCAG 57840
CCACTCACAC ATGGCGGGCT CAGCAGCCAC CGGCCCGCC CCTCCTCGTC GCCGAGTCG 57900

FIG. 6.22

CAACTGCGTC TCGGGCCACA GGGCGGACAG CCACGCCTCT GCGGAGGGCG ACCGGAAGTG 57960
CTCACGTCTT CACCTTCCCC GCCACGCCAC CGTCCTTTCA GGCCCAGCGT GCAGCAGGAA 58020
GGAGGACTCT TTTGCCGCGG ACTCAAGCCG GAAGCCGCCT TCCTAGTGGA GACGCGAGTG 58080
GGGGAGGAGC AGTCCGAGGG GAACGTGGGT TGAACGTTGC AACTAGGGTG GAGATCAAGC 58140
TGGAACAGGA GTTCCGATCG ACCCGGTACC AAGAAGGGGA GTGCCCGCGG CAGGTAAGGG 58200
AGAAGAGGGA GGGGTTTCTT TCCGCTCTCG AAATTGGGAA AAGAGACAGA GCTGGGATGA 58260
CCTATGGGGT AGTCGGCGCG CTGAAAGGAT GGGCTGGGCT GGGACGGGGT TCAAGTGGGA 58320
AAGGTTGATG ATTAAGGTAT AGAGTTGGAC TTACAGATCC GTTTGGGCGC AGAGAGGTGA 58380
ACGCTGAAGA GAAACCAGAG TTTGTTTTCG TTTTCCAAGG AGCGTGGAGA TGGGCAGGGT 58440
TAACGGACCC TCGCCTCCT TCGGCTTCTT AGTTTGGGTG TTGAAACTCA CCTCCTTTGG 58500
TCCTGTTCTG CTCTGATTCA AGACAGTTGG GTTTGGTACC TGACAGGGCT GGGTGCAGAA 58560
AGCTGACCCT GTTCCTCGGC TTCCAGGTCG GTTGTGGCCT CGCTTTTGAC AGTTCACGTG 58620
CCGAGCCTAC TCGCTCTCGG AGGGCGAGCT CAAATGGGTG GGTTTAAGGC CCCCTCTTCG 58680
AACAGCTGTT TCCCTGGGTT TCTCCATTTT GCACACAGGA GTGTGAATTA AGTTTAATTG 58740
AATACTTTT GCGATTCCCA GGGCCACCTT GACACGTTCA TTGTGCTATC TAACTGGGT 58800
CATGCTGGGC TAATAATTCA CATTAAAGGT TCTGGAGTAT AAGTGGTTCA CAGAAGTATG 58860
AAAAGGGGAT GTTAGAAGAA AGATGCTGGG GGTGAAGTAG AGTTGAGGAA GACAGAACTG 58920
GAAAGCTAGG TTGGTTTCAC AGTACAATGA GCTTTAGGTC ATAATACTAC CTTTAGGTTA 58980
TATTGGGCTG TTTGGACGGA GTTTGCTGTA ATCAGGCTAG AGTAAATAGA GAATTTTAAA 59040
CTAAGCATTG ACAGGCTCAG ACTTGTAGAG GCATCATTTT GACAGTGATA TGAAGGGAA 59100
AGAGGTAGAG ATTTGAGACC TTTCCAAAGA ACTGTCCACA GAATTTGGTG ACTTACTGTG 59160
CGAAGAGGGA AATAAAGAAT AGGGAACAAC TCAAGACTTT CTAGTCTGTG TGTTTGAAG 59220
GATGGAGACG CCCACATTTA AGTGAGATAT GGAAGGAGG AGCAGATTGT TTTGAAGGG 59280
AGGAAGAGCA GTTACTTAGG GTCAAATTA GTTGTAATAAT CCCCCCGGG ATTTTGTATG 59340
TAAGTCAAAG TGAATTGTAT TTGGAAGAAG AACTGGGGAG CCCACCTCTG GTATTTTTTT 59400
TATGTCCCTC ATATGGACAA ATAAACCTCT GGTATTAAAT GAATTTTCTT TTGGGGGATT 59460
CTATATATTC GGGATTTCAA CCACCAACCT ATCTGGTTTT TCCCGCTGAA ATGTTGGGTG 59520
ATGGAATCAG GAGAGCAGAT TTGGAGACTC TTTATATTTT ATAATTGAGA GAGACAAAGA 59580
GAAAACCGTT TGATTTGAAA AAGTTTTCTA GGTTCCCTCA GGTAGATGGA AATTTTCATC 59640
AAAAACAGTT TATTCAAGGT ACATAGCCTA CTAGTTTCCC ATTTGAGAGT ACCGCAGAAT 59700
GATACGACGT GTACTGCTT TCTACGCAGA ATGAAGTATA AAATTAGCAC CAAATAGTAA 59760
CTTTAATTTG TCAGGTGCTA AACTTTTTAC ATGCTTTATC TCATTTAATT CTTAGAAGAA 59820
ACTAATTTTA CAAGTAAGTG TCTGGACCAA CATCTGCAGG TACAAAGCCT GAAAAGCGTA 59880
AGTTTGACTC CTACATAGTT CTCTTTTGT AGTAGATTAT AAATAGAACC AGCCAAAGGT 59940
AATAAGTTGT CTGTGCCTAA AAAGAAAGAA AAAAGTTAGC ATCAGTAGTT CTCACCAGAA 60000
GGGGTGATT TGCTTACCAG GGGACATTTG GCAAGTCAGG AACTTTTTGG CTGTTGGATC 60060
TAGAGGGTAA AGGTCAGTGA CGCTGCTAAA CATCGTCAGT GCATAGAACA GCCTTCACAA 60120
ACAATTATTT GGTCAAAGAT ATTTGTAGTG CTGCAGTTGA GAAATTTCTG TCTTATGGTT 60180
ATTTCTTCAG GAATAGGAAA TTAAGATTCT CCGATACTTT CTTTAAAAAG CAGTTTTATT 60240
TTTGAAATTA TTCCTTGGCT TGAAAGGTTT GTGAAGTTTA TATAGCCGAA CCAGAATAGC 60300
GTAATTAGAT TTTAAAGTGA ATTGTGAGCC ATCGATTCCC AGGAGATGGG TGTATAGAA 60360
TCATGGATTG TTGGATTTGG GAAAGACTTA TGCCTAGAAT TATTTTACAA CATTTCTGCT 60420
AAGTGGTAAT TCTCCTCTGC CCTAAAGGTC TCTGTATTT GATTTTCTTA TCATTGTGAA 60480
CCCACAATTA AAATGCTCTT AATTATTTTT TGCTTACACT GAGCTCCGGT CTCTTGAAT 60540

FIG. 6.23

TTTACTCTG TTAAATGTGG TTCTGCACCA TAGGACTGCA CTCAAAACAA GCTTGCCACA 60600
TATGTAATTT GTACTAGGAC AGTGTTTATA TTTTGTTC AATAACAAAA TAAGTTAAAT 60660
GTGGTGTAAT TTAGATCATT TACAAATAAT AATTTGTTAG CAGCTTTTAA TAAGTAGTAT 60720
TTTCCCAAC TGGTGAAGTA TTAATGTTGG TAGTTGAAAA CAATAGGAAT GTATGGAATA 60780
TATGGTTCAC TGGTCTTTT GTTCCTGTCA AATAGTGGCA CAATGGATCT GGGGTTTTTC 60840
TCAGTATAAT GCTGGCATAT TTGTTTCAAA TTGTACATAG ACTCTAAAAA GTTAGGCTTT 60900
CAAATTCTGG TCAATATAGT TTGCTTTAAA TAGTAGCTGC CTCTACTACA AGTTTTATTT 60960
AATTTGTTGA CAAATGAGTC TGCTATGAAA ACCGGTCTCTG TTGCCAGTCA CTACCCTCTG 61020
TTCACAAATT TGCTGGGTTT ATAAATATAG GTATCATTTC CACTTCAAGA TTATAATTTT 61080
AGAATATGTT TATTCTAGGA CATATAGCCC TCAAAATCTG CTTACTATAT ACGTCTTATA 61140
AAATAGCATG GTTCTTTTTT ATAGTAAATA GAATTTTTAT TTAATTGTCT ATTGACTTTT 61200
TTTTCCAGG GTTCATTGAA AAAATCCTTA GTGATATTGA CATGTCTCAA GTGACATAAA 61260
TTAGCCAATG ACTCGGAATG ATGGATTCTC CGAAGATTGG AAATGGTTTG CCAGTGATTG 61320
GACCAGGGAC TGATATAGGG ATATCTTCAC TCCACATGGT GGGGTATTTG GGAAAAGTTA 61380
GTGAACCTAT TTTTGCCTG AGTGCAAAGT TTTTTTTTT TCTCTATTTT TGAGACTTAA 61440
ATTCAATTTT GATGTTACCA GTTAACCTCT AAAAAATTGT GTCTCCACG GAAATCTTAC 61500
AGTAATGGCG AAAGATTGTT TTAATGTGTT TACCTTTCTG TGTTTTATTG ATACATGAAA 61560
GTGGAAATAA AACATAGACC TTATGATTTA CTGTTCTTTG AAAATATGGT ACATAAATTC 61620
TCCCGGGTAA TTGATGTTAC TTTTTCCTT GCAAATAAAA TTGATACTAT TCTTAACACA 61680
TAAAATTTAA TATTTAAAC TATAACATAA TTCTTTTGG AATAATAGCT GTATTTAAAG 61740
GCTTATATGC ATTTCTTTT TTTGCCATGT TAAAATACC TTGTCAGGAT ACTTGTAATT 61800
GAAAATTATA ATTTTCTCTG GTTACCTTTC CATTTAACTT TTAATATTTT GATATATTCT 61860
AGGAATGTCT ATATTTTAAT TTGCTTTATT TCTCTTTTAG AATTTTGATT CAGCTAAAGT 61920
TCCATCAGAT GAGTATTGCC CTGCTGTAG AGAGAAGGGA AAGTTAAAAG CCTTAAAGAC 61980
TTACCGAATT AGTTTTCAAG AATCTATCTT TTTGTGTGAG GATCTGCAGG TAAAGTATTA 62040
ATCTTATATA GTATATATAA GATTTTCTT TTTTCTTTG CTTTTTTATT AATTGTTTTA 62100
AAAGTTTACT CATTTTTTGT TTTTLAGACT AGATTTTAA TATGTAATCT CAGTTTGTA 62160
GTCTGTCTGG TATACAATGT TATTTTCCA CCTACCTTTA CTTGGTTGCG TAAAGATGTT 62220
CGTTTTTATT GCCATTTGAT TTGCGAGAGG AGAAAATACA TTTCAAGGTT TTTTCTTTT 62280
TTTTAACCT TTTGGAGGTC CTTGTTAGCT ATTAGCATAT AGTAGTACT CTCTCATCTC 62340
TTTGGTTTAT CTTTGCACT GATGGGAAAA GTTATGAATT TCTAATGTAC CTGGAAGAGT 62400
ATTTTGAAA TTGGTTAGTC CAAAACCACT ATATATACTC TGAAGTAAAG AGAGTATAGA 62460
ATCTTGTAAT TTCTAAAAGA TCCTTTTAGA AGCTCTAAAT CGCTTTTAGA ATTATAGTAA 62520
TTTGTACCGA CTGGTACGGC TTTTATATAG CAGCTCATT AATTCTGTAA TACTCCACAT 62580
TTTATTGTAT TTGACAGTTT ATGAGACTGT CTCATACACT TTTAATTCTC AGAAGTTTGC 62640
AAGATTTGTA TTCCTATTTT ATGAATAAGA AAATAAATTG ATTTGAGAGG GTTTGGGAAC 62700
ATAAGATCCT GATACAGTGG CAGAGCTGTG GTTGAATAC AGACTTCTAA TTTGAGATCT 62760
GTTTATTCCA GCAAAAAATT AGCAGTTCAT CAGAATTACC TGGAGTGCTT TTAATAAATT 62820
TCTGAGTATC ACCCCCAGAT GCTGATTCAA TAGAGTTGGC CCAGAATTCT GTGGTTTTGT 62880
AACATTTGAG GATGAGTCTG ATCATCATCA GCCAGGTTTG GAAAATACTA GACTAAATCA 62940
CATGGTTGTT AATAGATACT TATGCTGGGT ATAATTTGAA GTAAAGTAAT CCCAGGCGTG 63000
TCTACAAATA TAAATTTCTT TATGTTTATA TTCAGTAATT TTTTATGA GTGTCAGTGT 63060
TTGGCACTGT TGCAGATACA ATGTTAGGAT ACAATAATAA AACAAAAATT TCTTGCCCTT 63120
AAGGAAGTTA TGTCATAGAG TGGGAAAGAC AGTGAACAAG TATGTGTTTT TCTGTCAGGT 63180

FIG. 6.24

GATAAAAAGT GCTGTGGAGA AAAATAAGGC AGTAGGGACT GGAATGCCAA AGTAGGGGGA 63240
GTTTGCAATT TTAATAGGA TGGTGAGGGG AACGCTTCAA TGAAAAGTGC AATTCGAGCA 63300
AAAGCCTGAA AGAGGTGAAG AGCAGTGAGC TTTCTAGGCA GGGGAAGCAA GTTCCAGGAA 63360
GGCCCTGAGA GAATGGAGGC TGCCTGTCAT GTTTGTGCTA CTGCAATGAA AGCAGCAGAG 63420
CGATAGAAGG TGGATCAGAA AAATAATGGG GGAGCTGGAC CAAGTAGGGT CTTATAAGCC 63480
ATTGTAAGCT TTCTGGCTTT TACTATGGGT GAAACCAGGA ACCATGGCAG AGATGTTGGC 63540
AGAGGAGTGA CATAAGTTGA CTTCAAGTGT AAAAGCATT CTGTGGCTGC ACTGTTGAAA 63600
ATATATGTAA TGGGCAAGAC CTGAAGCAGG GAGATTAGTT ATAGTATAAT ATGAATTATA 63660
TTTGGTCCTT GTCTATGGTT TCCGTTACAG AGCTAAAAGT CTTGGAATTT CCTGAATGAT 63720
AAGAGTGTCC TGTTATTCAG AATGAGCCTG TTTGCTAACA CCGGGGTTCA TACTATTGTG 63780
GTGACTTAGG ATGGAGCCGT AGATAGCCTC AGATGGGGCA AGTAGCTGGA AAGACCACAT 63840
GATTAGAGAA TTAACGGGTT AGAACTTTTA GCCCCACGTA CAGGCCTCCA GGAAAGGAGT 63900
GGAGGGGCTG GAGATCAAGC TGTATAAAAA TATCAAGATT TGGATTTAAT GAGTGGGTTG 63960
CTGGGGGCTG GTGCCGTGTA GGAGGTGGTA TGCTTAGAGG AAGTGGAAGC TTCATACCTC 64020
TTCTGTCCCA TACCTTGCCC TACTCATTTT TTCATCTATA CCCTTTATAA TATCCTTTAG 64080
GATAAACCAA TAAACATAAG TAAGTGTTTG TTTGAGTTCT GCGAGCTGTC CTTGCAAAC 64140
AGTTATGCCC AAGAAGGGGG AGTGGGAACC TTTGTAGCCA GTCAGTCAGA TGTACTGGTG 64200
GCCTGGATGT GGGATTGGCA TCTGAAGTGG AGGGAGTCAT GGGACTGAGC CCTCAACCTG 64260
TAGGATCTGA CATGGTCTCT AGGTAGATAA CATCCAAATG GAATTGGATT ATAGGATACC 64320
CATTTGGTGT CCTCTGGAGA ATTGCTTGGT GTGGGGAAAA AGCCCCCACA CATCTGGTCA 64380
CAAAAGTGTG CTGGGAGGAT AGAATATGTG AAAATTGTCA TAATCAAAAT GGAGTCACTT 64440
GTGTTAAAAA AGAAAAAAAA ATCCTGACTG GCCAGGCACA GTGGCTGACA ACTGTAATCC 64500
CAACACTTTG GGAGGCTGAG GCAGGAGGAT TGCTTGATCC CAGGAATTGG AGACCAGCCC 64560
ATGCAACATA GTGTGGCCTT GTCTCTACAA AAAAAAAT TAAATTAGC TGGGCATGGT 64620
GGTGTGAGTC TGTAGCCCCA GCTACCCGGG AGGGGGACTA CGGGTGCACG GCACCATGCC 64680
CAGGAGGTCC AGGCTGCAGT GAGCTGTGAT TGTGCCACTG CATTCCAGTC AGGATGACAG 64740
AGTGTGAGAC CCTGTCTCTA TAAAAGAAA AAAAAAGAC AAATAGATCC AGGAAAGGCT 64800
ATGAAGAGAG AGCTTTCATG CATAAATACC AAAATATCTC AAAAGACTCT GCAAAAACCA 64860
CACCTTGCA CAAAGGCCAT CATGAAATAC TTCTGAAATA CACAGAAAAT ACATCATGAA 64920
ATAAATACAC AGAAAATACT TCTGCAAGGA CATCTGCCCA GCAACTGCCT GGTCCATCTG 64980
TGGACGGGTG TCATCCTTGT TATTGATCCT TGTAGCCAAG GGTAATTATC TCAAAACAAG 65040
TATGTGATCC TCCTATTTT CCTTTAAAAA CCTTTTGTCT TCCCTTACCT CCCTGAACAC 65100
ACACAGTTTA CTATGGCATG TGTATTCCCA TTGGAATACT TTATTCCTGA ATAAATGTCA 65160
CTTTCTTTT AGAAGCTTCT CTTTCTTTT TATTTAGATT GATAAGTAGA AAGGAAAAA 65220
AGCTTTTTT CCTTTGGACT AGTTGAAGGC AGTTGCAGTA TTCTGGGGGA GAGGGTGGTG 65280
GCAGAGGTGT TGAGGCATGG TTGGAGTTA TTTATACTTT GAAGGTAAAG CCAACAGGAT 65340
TTGCTGAAAG ATTGGGATAT GGGGTTGGAA AGAGGAATCA AGGATAGTTC CAAGATTTT 65400
GGCTTGAAAA ATTAGAAGAA TGGAATCGTG AATTACTGAG CTGGGAAGAC TTGGAAGAGC 65460
AAGGTTTTGG GGAGAAGATC AGGACTGTAA GAATAGAGAA GTCCTTGTCC CCAGGAGTTA 65520
GGTTTTTGGC TATTAAAGTT AGATGTACTA CATAGATTTT TAGTTGGTTT TTTGTTTTT 65580
GTTTTTTTT TTTTTTTTT TGAGACGGAG TCTCGCTCTG TCACGAGGCT GGAGTGCAGT 65640
GGTGCGATCT CGGCTCACCG CAACCTCCGA CTCCCTGGTT CAAGGGATTG TCCTGCCTCA 65700
GCCTCCTCAG TAGGTGAGAT TACAGGCATG TGCCACCCAG CCCAGCTAAT TTTTGTATTT 65760
TTAGTAGAGA CGGGGTTTCA CTATGGCCAG GATGGGCTTG ATTTCTGAC CTCAGGTGAT 65820

FIG. 6.25

CCACCCACCT CGGCCTCCCA AAATGCTGGG GTTACAGGTG TGAGCCACCA CGCCCAGCCC 65880
GGAGTTTTGG TTTTGAAGC ATTCTTTTTC AAGTGATAAA GCAAAAAATA TATAATCAAG 65940
AATTTTAAGT ATATACTTTG GAAATGTAA AAAGGAACAT GAGTAATTTA TTATTATTTT 66000
TTTAATTTCT AGTCAGCAAT GAGAGCCCAG TGTACTTTAT GAAGTAGATT GGTTTACACC 66060
AGGAGTGAGC AGACATTTTG TATGATGCAC AAACAAGGAA TGATTTTTTT GTTTTTTAAA 66120
TGGTTAGGAA AATATCAAAA TAAAAAATGC CAGAAAAAAT CAAAAGAAGG GCCAGGTGCA 66180
GTGTTTCACA CCTGTAATCC CAGCACTTTG GGAGGCCAAG GTGGGTGGAT TCTCTTGAGG 66240
TCAGGAGTTC GAGACCAGCC TGGCCAACAT GGTGAAAACC TGTCTCTACT AAAAATACAA 66300
AATAGCCGGG TGTGGTGGCA TATGCCTGTA ATCCCAGCTA CTTGGGAGGC TGAGGCAGGA 66360
GAGTCGCTTG AAGCCAGTGG CAGAAGTTGC AGTGAGCCAA GATTGAGCC ACTGCACTCC 66420
AGCCTGGGCG ACAGAGGAGA CTCTATCTCA AAATAAATAA ATAAATAAAT AAATAAATAA 66480
ATAAATCAAA AGAAGAATAC CCTTTCATAA TATGTGAAAA TTAAATGAAA TTCAAATTTT 66540
AGTGTTTATA AATAAAGTTT TACCGGAACA TAGCCATGCT CAATCATTTA TGTATTGTTT 66600
ATGGCTTCTT TTGCATACAA CAACAGAGTT GGGTAGTTGT GACAGACTAT GTAGCTCATA 66660
AAATCTAAAT ATTTATTATC TAGCCCTTTA TCAGTAAACT TTGCTGATCC CTGTATAAGT 66720
CCTCTGAATC AAATTATTTT CAAAGAGTTC CGTTATAAAA TTTGGAGTTT ACTCTGCTGT 66780
AAATTGCAAA GAACCATTTG GAAAACCTCT TTAGTCAGG TATTTACATT AAAATGTTCC 66840
TTGATTTGTA AACACTAATA TTCAAGACTG GTCCAAAATT ATACCAAATT GAACTCTCA 66900
AGTGTTTTTA AACAGTAGGA AGTTTTAACT TTTTTTTTTT CGTGGAGTAG TCTATCATTC 66960
AGCGTTTACT TTGGAACATT TAATTAGTCT TTTTAAAAA CCCATGAAAT TTATAATAAA 67020
AATTTTAAAT CATTAATGTT GAGTAATCAA AGAAAACCTT TTTTGTTTTT TCCATTTGTA 67080
AAATGAGTAC ATTATTATTA TAATTTGTCT TTGGCCATAC CTTGTTGATA ATTACTTATA 67140
CAAGTATAAG AAGACATGGT ATGTTTTCTT TTTTCTTATT TCACAAGAAT AAGTACAGGA 67200
ATTTACTTAA GCTGCTCCAA AACTCAGTGA AAGAGACAGG ATTAGGTTTT TTTAGCATT 67260
GGATTTTAAA TGATACTAGA TGGTTGCGCT GGGCTAAAT ACTAATGCTT TGTGTATATT 67320
TTTATGACTT TTTTGAAGAC AGCTTAAAAG CTTTATTCTA GTTATAAAAA TGATACATGT 67380
TCACTGTAAA TAGAAACAAG TCAGGTATAC AGAGATACAA ATATTTAGAA CATGTGAAAA 67440
GAGGCAACAA AATTTTATAA AAAGAAAAAA GATAAAATC TGAAATCATT AATTTATAAG 67500
GGAAAAATCA GGGCAAGGAC AAATTATATT ACAGATTGGC CTATGGTGGG AGCACAGATT 67560
ATATAGAGAA AAGTCAGTGA AGACACTTGC GAAGAGTGTG GGTGGAATC ACTAAGTTTT 67620
GCAGTCCCGG GGCCTCTTAT GGTATTATAC TGTTTTGTTT TTTTTTTTTT TTTAATATGC 67680
ATTCCTTTGG AACCAAGGGT TTATTATGTT TTGAATAAAG TAGAGGTGTA AGTAGGATGC 67740
ATATACCATG ATCTTGACTA CTTGAGATTG ACAAAGGGTT TTCGTCTCAG GATTTTTTTT 67800
TCTCTTAAAA AAATTTGTAT TAATTTTAA ATTGTAAAAA AATTCATCAA CTTAACCATT 67860
TTTATGTATA GAGTTCAGGA GTATTAGGTA TATTCAGTTG TGCAGCAGAT CTCTAGAACT 67920
TTTTTCATCT TGCAAACTG AAACCTGTGA CCCATTAAAC AACCACTTCC CATTTTCCTC 67980
TCCCCAGCT TCTGGCAACC ATTCTAGTTT CTGTTTCTT TCTTTTTTTT TCTTTTGAGA 68040
TGGAGTCTCT GTCGCCAGG CTGGAGTGA GTGGCATGAT CTCGGCTCGC TGCAACTTCT 68100
GCCTGCGGGT TCAAGCAGTT CTCCTCCCTC AGCCTCCTGA GTAGCTGGGA CTACAGGGGT 68160
GCACCACCAT GCCTGGCTAA TTTTTTTTTT TTTTTTTTTT TTTGTATTT TAGTAGAGAC 68220
GGGGTTTCA CCATGTTGGC CAGGCTGGTC TCGAACTCCT GACCTCAGGT GTTCTGCCTG 68280
CCTCAGCCTC CCAAAGTGCT GGGATTACAG GCTTGAGCCA CTGTACCCGG CCTCTAGTTT 68340
ATGTTTCTAT GAATCAGACT CAGTACCTCA TATAACGGA ATCATACAGT ATTTGCCTTT 68400
TTTGTGACTG GCTTATTTCA CTTGGCATAA TGGCCTCAAG ATTCATCCAT GTTGTAGCAT 68460

FIG. 6.26

GGATGAATAT ACAGTTAGGA GTTCCTTTTC TTTTAAAGT CTTAATCTCC AGTTTATTTT 68520
TGTTTATTTA TTTATTTTAT TATACTTTAA GTTCTGGGAT ACATGTGCAG AACGTGCAGG 68580
CTTGTTACAT AGGTATACAC GTGCCATGGT GGTGTTGTC ACCTGTCAGC CTGTCATCTA 68640
CGTTAGGTAT TTCTCCTAAT GCTATCCCTC CCCTAGCCCC CTACCCGCCG ACAGGCCCGG 68700
GTGTGTGATG TTCCCCTCTC TGTGTCCGTG TGTTCTCATT GTTCAGCTCC CACTTACGAG 68760
TGAGAACATG CGGTGTTTGG TTTTCTGTTC CTGTGTTAGT TTGCTGAGAA TGATGGTTTC 68820
CAGCTTCATC CATGTCTCTG CAAAGGACAT GAGGAGTTTC TTACTTTTAA GGTTGAGTAA 68880
TATCCACAT TATGTGTATG CCACATTTTC TTTATCCATT CACCTATCTG CAGATGTTTG 68940
AGTTGCTTTC ACTTTTTGGG AATTGTGAAT AATGCTGCAG TGAATGTGGG TGTGCAGGTA 69000
CCTTTTCAAG ATTCTGCTTT TGAGTTTTTT TTGGATACGT ACCTTTTTAT GATGCTTTAA 69060
ATACATATAT GCTATTTTTA AAGGATTCTC AGTTTTCTGA CATATGATAG GACTTAGGAA 69120
GTAATCTCAA AGCATCATGT TGACAGGTTG TTAGTTGATG GTGACTGCAG CTAGTTGGAA 69180
AGTCAGAAGA ATCTAGAAGT TGTCCATTTA TACTAAAGAA TTTCATAGTA AGTGCAGTAT 69240
TATGAGTGTA ATGTTCAATT GGTAGAAGAG GCTATCTGAG GGGATTTAGT GCATTTCACT 69300
TATCTGTTGG TGTGAAACGA ATCACCTTGA AACTTAGTCG CTCAAAAATT TTAATGGTGG 69360
CTGGGCATGG TGGCTCACAT CTGGAACCTC AGCACTTTGG GAGGCCGAGG CAGGCAGATT 69420
GCTTGAACCC AGGAGTTTGA GAGCAGCCTG GGCAACGTGG TGAAACCTTG TCTCTACAGA 69480
AAATACCGTG GCAGGCGCCT TTAGCACCAG CTACTTGGGA GGCTAAGGTT GTAGGATCTC 69540
TTGATCCCAG GAGGCAGAGG TTGCAGTGAG CTGGGATCGT GCCACTATAC TCCAGCCTGG 69600
ATAACAGAGC CAGACCCTGT CTCAAAAAAA AATTTTAATG GCTCCATTTA TTATTTTACA 69660
TGATTATGTG AGTTGACTAG GGAATTCTTA CACATCACAC CATGTCAGCT GGGACAGCTG 69720
AAATGTCCAC ATGGCTGGCA GTTGGTACTA GCTGCTAGCT GGAAGTTGAG TTCAAATAGT 69780
CAGCCAGGGG TCTCAGTTAT TTTCCATGAG GTTCTCTCCA TGAGGCCAGC TGGGCTCTTC 69840
ACAGTGTGAT AGCTGGGACT AAGAAGGAGT GTTCAGAAG AAGGGCTTGT CCTCTTGAGC 69900
CAGTGCTTAT CAGGCCTCTA TGTATATCAT GTGTGCTAAT GTTCCATCAA AGCTAGTCAC 69960
AGGGCCAAGC CAACTCTGTA CAGTGTAGGG ACTGGCTGCA GGAGGGCATG AATTACCAGG 70020
AGGTGTAGTT CTCTAGTTCA TAGGGAGGGC CATCAAGATA GTAGTCTACC ATACTTGTGT 70080
AAAAGAAGGC ATTAATTAAC TATTATTATT ATTATTATTA TTATTTTAGA GACAGGGTCT 70140
TGCTCTGTTG CCCAGGCTGG AGCAGTAGAG TGGGGCAATC ATAGCTCATT GCAGCCTCCA 70200
ACTCCTGGGC TTAAGCAATC CTCCCATCTC AGCCTCCCAA GTAGCTGGGA ATACGGGAGT 70260
GTACTGCCAT GCCACCTGA AAAAGAAGGC ATATTTTAAA AGCAGACCTT TAGTGTAGAG 70320
GGTTCTTGAA TTTGTTATTT AAAATATTCT GGTAGTTTTT AAACCTAGGA AAGACCCACT 70380
GATTCTTTTA GTGATATGTT TACATTGTTG TTATTTGGCA TAAATTGTGT TAATGCACAG 70440
TAAGATTTCA TGAAGTCATT AAAATTCAGC CACTTGGACT CTAAACCCAA TAAAGATGTA 70500
AAACAGCAGT GCTATGAGAT GCATATTCAG TTTCAAATA TAGGAAACAC AGAAATTACT 70560
CTGTGCACTT TTAATTTGAA AATACTTTTA AAATGTGTAG TATAATGTAG TGTCTGTCCC 70620
AAAAGAGTAA CATTCAATTAT AGTGTTTCTT TACGTTGTTG AAAATTTTAA ATTCACTTAA 70680
CATTAGATTT TTATTAAAGC AAAAATATGT TTTCTTATT AGCTTACCCT TTTGTAAGTC 70740
AGATTAAACC CTTGATTGTT CAAATTAACC TGAAAAAAT TATTCTTTTG GAGGCCAAAC 70800
TTTTGATTAA GTAGTTGTTT GTCTCTAATT TTTCAAATT TATGTGTATA AATATAACCT 70860
GTCATCAAAT CAATGCTAAC ATTCTATACA TGTTTTTCAT GATATGAAAA CTATAAAACA 70920
TGAAGTTATT TGAATTTGTG TAGTTTTTAT CATTTTATTT TTACTTTCCA GTGCATCTAT 70980
CCTTTGGGCT CTAAATCACT TAATAACCTA ATTTCTCCTG ATTTGGAAGA ATGTCACACT 71040
CCACATAAGC CTCAGAAAAG GAAGAGCTTA GAAAGCAGCT ATAAGGATTC ACTTCTTTTA 71100

FIG. 6.27

GCAAATTCCA AAAAGACTAG AAATTATATT GCTATTGACG GTGGAAAAGT TTTGAACAGC 71160
AAACATAATG GAGAAGTATA TGACGAAACC TCGTCAAAC TACCTGATAG TAGTGGTCAA 71220
CAGAATCCAA TTAGGACAGC TGATTCCTTG GAGCGGAATG AGATTTTGGA AGCTGATACT 71280
GTTGACATGG CTAATAACAA AGATCCTGCT ACAGTTGATG TCTCTGGAAC TGGCAGACCT 71340
TCCCCTCAAA ATGAAGGATG TACATCTAAA CTGGAAATGC CACTGGAGAG CAAATGTACA 71400
TCATTTCCCC AGGCTTTATG TGTCCAGTGG AAAAATGCTT ATGCTCTCTG TTGGTTAGAC 71460
TGTATCCTGT CAGCTTTGGT GCACTCGGAA GAGTTAAAGA ACACCGTGAC TGGACTGTGC 71520
TCGAAGGAGG AATCTATATT CTGGCGGTTG CTTACAAAAT ATAATCAAGC AAATACACTT 71580
CTATATACCA GTCAATTGAG TGGTGTTAAA GGTTGGTACT AATATTTTAT TTTTATTTAC 71640
TTATTTATTC ATCTGGAGTC AGGGTCTCAT TCTGTCACCC AGGCTGGAGT GCAGTGGCAT 71700
GATCATGTCT CTTGACAGCC TTGACTTCCC TGGCTCAGGT GGGCCTCCCA CCTCAGTCTC 71760
CCAAGTAGCT GGAACACAG TCGTGCACCA CCATAGCCAG CTAAGATAGT GAGATGGTGG 71820
CCCCACTGTC TTGCCAGGC TGGACTCGAT TTCCTGGGTG CAAGCACCCCT TCCCGCCTCA 71880
GCCTCCCAAA GTGCTGGGAT TACAGGCATG AGTCACCATT CCAGCCTACT TGTCTTTAAT 71940
TCTTAAAAAT ATTAATGTTG AGTTTGTCT CCCAGCATGT GGGAAAGATG TCATCCATTG 72000
CTTCTGTTTC CTGGAGGCCT GGGAGCAAGG AGCCAGGAA CAGTATCACG AAGCTTGAGA 72060
TAATACCACT TACATTATCC TGAATGCCCC AAAGGCAGTT TTTTGTGTTT TTTTGTGTTT 72120
ACTTTAAGTT CTGGGGTACA TGTGCAGAAC GTGCAGTTT GTTACATAGG TATACGTGTG 72180
CCATGGTGGT TTGTTGCACC CATCAACCCG TCACCTATAT TAGGTATTTT TCCTAATGCT 72240
GTCCTTCCCC AACCCCTCCA TTCCCCATCA GGCCCCAGTG TGTGATGTTT CCCTCCCTGT 72300
GTCCATGTGT TCTCATTGTT CAACTGTAC TTATGAGTGA GAATATATGG TGTTTGGTTT 72360
TTTGTCTTGT TGTTAGTTTG CTGAGAATGA TGGTTCCAG CTTTATCCAT GTCCCTGCAA 72420
AGGACATGAA CTCATCCTTT TTTATGGCTG CATAGTATTC TATGGTGTAT ATGTGCCACA 72480
TTTTCTTTAT CCAGTCTATC ATTGATGGG ATTTGGGTG GTTCCAAGTC TTTGCTATTG 72540
TGATTTTTTT TTTTTTTTTT TTTTTTTTAA GACAGAGCCT CACTCTGTTG CCCAGGCTGG 72600
AGTGCGATGG CATGATCTCA GCTCACTGCA ACCTCCGCCT CTCAGGTTCA AGCAATTCTT 72660
CTGCCTCAGC CTCCCAAGTA GCTGGGACTA CAGGCGCCCA CCACCAGGCC CAGCTAATTT 72720
TTGTATTTT AGTAGAGACA GGGTTTCACC ATGTTGGTCA GGCTGGTCTT GAACTCCAGA 72780
CCTCATGATC TGCCTGCCTT GGCCCTCCCA AGTGCTGAAA TTACAGGTGT GAGCCACCAT 72840
ACCTGGCCTA GGCAGTCTTT TTCAAACTC TAAGACTGTG CTTGTGTCTC AGGGTGTGAG 72900
GATAATAGTG GTTAGTTTAA AGTGTTTAAA CTAATGAAAA GCAGAATGAA GAAGTGAGTA 72960
AAAATCACCC ATAATCACAC AACCTCCTAA GATCTCTTGG CACAATAAGG GATATGTTTT 73020
TCATTTTATT CTCTGTAAAA TAGGATACTT ATGAACCCAC CTCCCAACAC AGGAAGAATT 73080
AAAACATTCC CAATAACTTA CATTTACCTA TGCCTTTCCT CCCATCCCAT TCTCTACCTC 73140
CCCCCATATA GTAATCATT TCTGAAATGT GTTTCATCAT TCCATCTTTT CTTAGTTTTT 73200
CTTACATGTG TTTATCTAAA CAGTATACAG TAGTCTCCCC TTATTGTAGT TGTACTTTTC 73260
TTGGTTTCAT TTAACCCGAG GTCTGAAAGT AGATGAGTAT AGTACAGTAA TATATTTTGA 73320
GAGAGAGGGA GACCACATTC ACATAACTTT CATTACAGCA TATTGTTATA ATTGTTGTAT 73380
TTTATTATTA GTTTAATCT TACTATGCCT AATTATAAAA CTTGATCATA GGTATGTAGT 73440
TATAGGAAAA AGCATAATAT ATAAAATGTT TAGTTACTAT CCAAGGTTTT AGGCATCCAC 73500
TGGGGTCTTG GAAGGTATCC CTCTCAGATA ATGGGGGATG GATGGTACTG AACCCGTGAT 73560
ATACAATGTT TTTCCCTATA CATAATAAT TATGATCAAG TTTAATTAAG AGTAAATTAA 73620
ATGTGGGCCA GGTGCAGTGG CTCACATCTG TAATCCAGC ACTTTAGGAA GCTGAAGCGG 73680
GCAGATCTCA TGAGGTCAAG AGTTCGAGAC CAGCCTGGCC AACATGGTGA AACCCCATCT 73740

FIG. 6.28

CTACTAAAA ATACAAAAAT TGGCTGGCTA TGGTGGCACA CGCCTGTAGT CACAGCTACT 73800
CTGGGAGGTT GAGGCAGGAG AATTGCTTGA ACCCAGGAGG TGGAAGTTGA ACAATCACTT 73860
GAACCTGGGA TCACGCCACT GCACTCCAAC CTGCCTGGGT GATAGAATGA GACTCTGTCT 73920
CAAAAAAAAA AAAAAAAAAA AAAAAGTAAA GTAAATGTGG CTCAACATGT TGCTGTCACT 73980
TGGAACATTT GTTCTGATC GTGTCTTCCA CCCACAAATT GAATGCTTTT TCCATCTTAA 74040
CACTTATCAG GCACTGTGGC CATAACTTGA GCAGTTGAGA TGCAACAGCA AAATTAGCAC 74100
AAATTTCTTT TTCTTTCTTC GCAGTTTCAT GGATAAGAGA TTTGTTCTTA GATCTCAGCA 74160
ACCTCAGCAT ATGATTTTTT TCTTTAAGTT GAGAACTTTG ACCTTTTTAC TTAGAGAAGC 74220
ATTTTACAGC TTCTCTTTGG CATATCTGAA TTGCCAGCAT TACTATGCTC GTGCTTTGGG 74280
GCCATTATTA AGTCAAATAA GGGTTGCTTG AACACAAGCA CTGCAATACC ATGGCAATAG 74340
ATCGCATCAC CAAGATGGCT GCTAAGTGAA CCACAGGCAG GAGTGTAGAC AGCATGGACA 74400
CATTAGACGA AGGGAAGATT CACGTTGCCA GTGGAACACA GCAGGACAGC AAGAGAGTTC 74460
ATGATGCTAC TCAGAAATGGC ATGAAATTTA AAGCTTATAA ATTGTTTCTG GAATTTTCCG 74520
CTTAATATTT TCAGACCACG GTTGAGTTCA GGTAAGTGAA ACCATAGGAA GCAAAACACG 74580
GATGAAGAGG GACCACTTCG TATTGCCTAA TTAGTTTGT TTTGATCTTC TGGGACCTTT 74640
TTTTCTTGTT GTAAAAATTT ATGGGGCTGT TTATAGTTGT GGCTCATTGA TTTTTCATTG 74700
CTACATAATA CTTCCATTTT GTAAATATAA CAGAATATTC ATCTACCTGT CAGTGGACAG 74760
TGGGGTTTTT TTGCCATTAT AAATGCTGCT GCTGTGACCA TTTGGGGGGC AAGTCTCCTG 74820
GGGCACAGTA TGAGTTTCCC TTCTGTATAA CAAAGGAATG GAAAATTATA GACTTTCGTG 74880
TCCAAATTTA CAAGATAATG ACAATTGTTT TCCAAAGTGG TTGTACCAAG CAATTCTCCC 74940
ATTAATAGTG TATATAAGAG GTCTTCCTGA TCCATATATT CTTCTTGGTT TATTTTCACA 75000
CTTTTGAGAT TTTTGCTATT TGAGTGGTAT AAAATGGTCT GTGATCTTGA TTTGCCGTTT 75060
CCACATTTTG AAGAGGTTGT CGGCTCTATG TGTATATATT GCTCATATTT GTTCCCTCTT 75120
CTGTGAAATG CCTTTTGAT CTTATCCCTA TTTGTTCTGT TCTGTTGATT GTCACGTTTT 75180
AATTGATTTG TATGAGTTTG TTCCTTGAT CATTGTTGCT AGAGTTACAT CAGATGTGTT 75240
GCTGAATCTG CTCCCAGTTT GCAGCTTGTT TTTTACTTT TAAAAACTG TCTTGATTTA 75300
TAGGGAAGTC TTTATCTTTT CATTTGGAGC TAGTAATGTT TGTGGCTTTT TAAAGAAATT 75360
ATTACTATTC CCAAGGTCAG AAAATCATTC ACCTATATTT TAACTGAAAA GTTATAAAGT 75420
TTTGCTTTTG ACATTGAAAT TTCTCATTCA GTTGGAAATC ATATTGATGT GTGGTATGAG 75480
GTAAGGATCC ATTTTTTTCC CATTTGCATA GCCAGTTTTT GTAGCTCCAC TTTATTTTCT 75540
CACTTGATCT GCCATGCCAC CTCTAGCATG TATCAACATA TCATGTATGT GTGCAGCTGT 75600
TCCTTAACTC TCAATTTTAT TCTCTTGGTT ACTTTGTCTA ACCCAGCACT CATACTTTTT 75660
AAATTATTAT GGCTACCTTG TAGGGCAAGA ATCCTCACTT TTATTCAACT TCTTTGAAG 75720
TGTCTTGATG CATATTTTTT CTGATCTTAC TTGGCCATAT ATATTTTGGG GACAGATGTG 75780
ACATCATACC AAGCTTTCTT TGCTTGACAT TGAGATATT TTCTTATTCA TTAATGTGCT 75840
AAAAATTTTG AGTTTGGTCA TACAGTCTTT TATATGGATC TTATACATCG TTTCCCTCTT 75900
GTTAACCATT CAGGCTGTTA CTAGTTTTTG CTGTTGTGAA TTAACACCAG GACAAATATC 75960
CATATATCTT TTGAATTAAT TACTGACTAG TTTCTAGGA AAGATATTAG AATATGAATA 76020
TTAAAGGTCT TGCTGAATAC AGTTTTCAGA ATGGTTGTAC CAATATATAA TTCCATTTTC 76080
ATTATGTAGA AAAAATACCT CAGTGTTTTT TAACCACCTT TGGTTAGAAC ATTCAAGACG 76140
TTATGGTTTT GTTAGGTAAG AAATATTTTG TTTCAAGTGA GGTTTTCTTT GAGACTGAAC 76200
TTTTTTGTGT GTGTCAGTCA TTTACAGTTT TTTGCAATTT TAAAAATTCA GTTTCTCACA 76260
AGCATTTTGC CTTTGACTTT TCTTCTATTT CTGCTTCTC TAATTACAGA AACCCCACTG 76320
TTAAGTAGGT GACAGTTCAG TTGTTTGCTG CAGAAGAGCA GCAGTTCAAT ATTGGAATTA 76380

FIG. 6.29

ACTTTAATTT TATGTTTTTA ATCTGTTACT AATTTTTTAC AGAATAATTG TAGTTTTTAT 76440
AATCTGGTTA ATTATATGTT TGAGCTGCAT TACTTTGCAA TGTAAGTTTT TTTTTTTGGC 76500
ATGGTCAAAT AACAAAAATT CTGGTTAATG CTTATTTTCAT ATTACAGGAG AATCCAGATA 76560
TTTCATTAGG GAAACATATA AGCAGAGTGT GATCAGGCTG TATGAATTAT TTATAAGAGA 76620
TGTGAGTGAA AAGATCTATT TGTAGCTTAA GAGTAAGTAG AGTCAGATGC ATGTAGAGTC 76680
TTTTATTCAA AATAATTTTC TTATTAATCT TGGATAGTTT CTTGTCACAG TAATTCCATT 76740
TTGAAGATAA TAAATATTAC CATAAAGAAG TGATCAAAAA CATAGATATG TGTGCCCAAA 76800
GGTATTTATC ACAATAGTAT TTATAAGTAT GAAAAAGAA ACAACTAAAA TGCTGGCAA 76860
TAGGAGAATG ATTAATAAAG CGATGTTTCA GCTGAATATA GTGGCATGCG CCTGTAAGCC 76920
CAGCTACTCA GGAGGTTGAG GCTGCAAGAT GGCTTGAGCC CAGGAGTTAA TGACCAGCCC 76980
AGGCAACATA GCAAGACCCT GTCTCCAAAC ACACAAACAC ACACACAAGT GCTATGTTTC 77040
AGTCACTGTA TAATACTAG CCAGATTTTT TGTTGTTGTT GTTTTGTTTT TGTTTTTGTT 77100
TTTTGAGAGA GCATCTCACT TGCCCAGGCT GGAGTGCACT AGTACAATCA CAGCTCACTG 77160
CAGCTTGTAG AACCTAACC CTCCTGGGCT CAAATGATCC TCCCACCTCA GCCTCCTGAG 77220
TAGCTGGGAC TACGGGTGGG TACCACCATA CCCAGCTTTT TTTCTAAGAG ATAGGGGTTT 77280
CACTATGTTG CCCAGGCTGG TCAGTTTTTA ATGAAGCACA TTTGTGTAGA CAAAGCAGGA 77340
TGTGGAACCG GATAAACACT ATGTTGCCAC TGAAGACCCC TTCAAACCCC TCAAAAATGA 77400
CATAGAAGGG AAATATGAGA TATTAGTTTG GGAAATAATT GTAACCTTAT TAAGACTCCT 77460
TATAAATTTA TCTGTTCTTA TGACCTGGCT AAGTTCAATA AAAGTTACAC AGAGTGGAAT 77520
AAATGGTTAG ACATCATTTG TAGTATAAGT AATTGCACAT AAGGAGGTAA CTTTAGCTGT 77580
TTTAGAGATA GACATAGTAT CTGAAAGGTT AGTTATTTTA CTAGACCTGT GATTATTTGG 77640
GTGAGAAAGG CTTTCACTGA GATTTTACCC ATTCAGTAAG TACTAATGAT ATTGTGCTGA 77700
TAGCATATAT TAAGGGAATA TATGGTATAC CACAGAGAAA GAATTAAGGA AATTTTGTGT 77760
TTTGCTTTTT GTCTGTTTGC AAACTTACT GACTCAGCTT TCATTCTTGG GAATGTGTCA 77820
GTTTTCTGTG GGAAGATATA CATTGATGAG GAATTGATAA TGTTCTCTGT ATTTTCTTAG 77880
ATGGAGATTG TAAAAAATT ACCTCAGAAA TATTGTCAGA GATAGAGACC TGTCTGAATG 77940
AAGTTAGAGA TGAAATTTTT ATTAGCCTTC AGCCCCAGCT TAGATGCACA TTAGGTAAGT 78000
AATTGGTAAA ACTTACTTGT ATTATACTCA TCTACCATAT AGAAATATGT ACCTCATAAG 78060
GAAATATAAT ACTGTTTGAT TACCTTGGAT GATCATATTC TTGGGAGAGA GAATCTGAGT 78120
AGTTTGACTT AGGAATCTAC CACTGGGTAA GTTATTGTAG GGCAGAGCTG TTCCATATAA 78180
ATATGTAGGC TGGTGTCCA CCTCTTGAGA GTGGGTGCAG TTCTCAGAAC CAGGAGAATT 78240
TTAGGGGGCA TATCATTAGT TGCTTCTCTA GTACGTTTCC TAGTAGACAG ATCTAGCATT 78300
TTTAACCTCA ATTGTGCATT AAAAAGCACC GAGGGAATTT AAAAGTAAAT GCCAATGCTG 78360
GGGCATTTGA ATTAGGATCT CAGGGATGGG GCTCAGGAAA TCAGTAATTT TTAGAAACCC 78420
CACATGATTG TTATATGTAC CCAGGGTTTA GAATCTCATC TAAACCAACC ATAGTAATTC 78480
TACTTCCCTA CCAGTGATTG GTTTAGGAAT GTCCTTGTGG TAGAGTTTTG GCCAGTGGAT 78540
ATTAAGAGAA ATATGCTGAT GGCCTTTTGG GAAAGCTTCC TCGCCTTAG AAAGGGCACA 78600
AGGATGGGAC CTCTTTGTTT TCTGTGACTT GGTTTTTGGC CTGTGGGAGT GGCCTGCAGC 78660
AAGTGAGCTA GAGAGTCTGT CCAAACCTTT CTAAATTTTT TTAGTATTGC GAAAAGGAGC 78720
TGCGGGGTTT TTTTGTGTTT TTTTGTGTTT AAAGGGCTTT TTGTTTTATT TTTCTTGAT 78780
CCTTGATTA ACTCTTCTAT TAATGTTATA GTAGCAGAAT ATGATACTCC CTATTAGTAA 78840
TAACCCATAT TATGTAAAAT ATCAGTGCCT TCTAGTTTTT CTCTCAATGA GTGACATTTA 78900
ACTTATATTA AAAAATGATA TTTATATTTT ATAATAAAAT CAGTTGTTGC TACTGATTTG 78960
TCTAGCATGT ACAAAGACA CCATGCTTCC AGATCATTAT AAAATATGAT ATTTTATAAT 79020

FIG. 6.30

ATATTTACAA TATATTTATA ACATATTTAT ATACTTAGAA TATATTTTAT AAGGCTGGGC 79080
TTGGTGGCTC ATGCTTGTA TCCCAGCACT TTGGGAGGCC AAGGCAGGCG TATCACAAGG 79140
TCAAGAGATT GAGACCATCC TGGCCAACAT GGTGAAACCC TGTCTCTACT AAAAATACAA 79200
AAATTAGCCG GCGTGGTAG TGTGTGCCTG TAGTTCCAGC TACTCGGGAG GCTGAGGCAG 79260
GAGAATCGCT TGAACCTGGG AGACAGAGGT TGCAGTGAGC TGAGATCACG CCATTGCATT 79320
CCAGCCTGGG GACAGAGCGA GACTCCGTCT CAAAAAATGT ATATATATAT ATATATATAT 79380
ATGTGTGTAT GTGTGTGTAT GTGCGTGTGT ATATATATAT ATCGGGAAGC ATGGCATCTT 79440
TTGTACATGC TGGACAGCTT TTGACGACT TCTTTGACTC ATGCTTCTGC CCCCTAATTT 79500
TCACTTTTTT TCCTACATTT TATTAAAATT AATATATAAT AGTTGTATAT CTGCTTTATT 79560
TTTCATGGAC TTATACATAC ATATTTATTC TGTTCTTATA AAAGTCTGAT TTTTCGTATG 79620
CCAAATTTCT GACATTTCTT CCTCTAGGCC TGAAGAACTG TTGTAATTTA TGCATCAGAT 79680
AGGCCCTCAG ATGGAATGAA TATTCTTTTT TCTTTATATC AAGGTGTAAT TTACATATAG 79740
TAAGACCGTT TTTAAGTGTG TACAGCTCTG TAACCCTCAC TACAATCAAG ATATAGGACT 79800
CTGTCACTCT AAAACTTCTC ACCAGGTTCA TCACCCCAAG CCACTGATCT GTTGAGCGAA 79860
TACTCATTTC AAAGGAGCTT TTTCCGTAAG ATCCCTAGAG TTAGATGGA AGGGCTTTCG 79920
TGGTGCATTT AGCAGATACC ATTTCCCTTC TAGACTCCCT ACTTCAGTTC CCAAGTGAAT 79980
TAAAGAATGG TTTCTCCCCC AGCCTGAGTC ACTACCTTC TTATCCCTGA TAATTATTTT 80040
TGGAACAAAG TTACATCTTT TGCTCCACCT CCGCCATGGG CCTGGTTTTT TATGTAACAG 80100
AAGGAATTTT TAAATTATTG TTTTGTGTAA TCATAATAAT TGGGCAAGCA TACAGCTCTT 80160
TTCAGTGCAG GAGGATTCCT CTCTTGTTTT ACTGCCCAT CAAGGATAGG TGCTATATTT 80220
TAGCTGAAGA TCTACTAAT GAAATGCTCT GTAATCATAT AACTTATTTA AAGATGTGTT 80280
TTGAGCTCTT TCATAATATT TTAATTCATG GAGAACTTTA TGTATTTTAG ACCTGAAGAT 80340
TTTATATTGT CATTATGAAA TGTAAATTGT TTGCTTTTTT AGTTAATATA TAGTTACAAT 80400
AGAATACGGA TTTAAAGGCT GATAATGAAT TACAAAATTG TGCTATATGA CATACTGTTT 80460
ATGCATACAG TGTTGCATAT TTTCATTTCT AGGATATTGA TTTGTATTTT TACTTACAAA 80520
AAAACTTTTT AAAACTTATT TTATGGCTGG GCCCGGTGGC TCACACCTGT AATCCCAGCA 80580
CTTTGGGAGG CCGAGGCGGG TGGATCACCT GAGGTCAGGA GTTCAAGATC AGCCTGGCCA 80640
ACATGGTGAA ACCCTGTCTC TACTAAAAAT AAAAAAATT AGCCGGACGT GGTGTAGGTG 80700
CCTGTAATCC CAGCTACTCG GGAGGCTGAG GCAGGAAAAT TGCTGAAAC CAGGAGGCAG 80760
TGTTGTCAGC GAGCAGAGAT TGCGCCATTG CACTCCAACC TGAGCAACAA GTGCGAAACT 80820
CCTTCTCAAA AAGAAACAAA AAAACTTTTT TTAATGTTTT TGTTCAAAG TAGCAGTGAG 80880
ACTATCCCGC AAAGGTGACT ACTAAAATAG CCTTTGTAAC TACTGATATT TATAGAATAT 80940
GCTTAGGGTT AGGGTATAAC TCGCTTGTAT TATACTCATC TACCATGTAG AAATATGTAC 81000
ATCATAAGGA AATATAATAC TGTTTGATTA CCTTGGATGA TCATATTCTT GGGAGAGAGA 81060
ATCTGAGTAG TTTGACTTAG GAATCTACCA CTGGGTAAGT TATTGTAGGG CAGAGCTGTT 81120
CCATATAAAT ATGTAGGCTG GTGTTCCACC TCTTGAGAGT GGGTGCAGTT CTCAGAACCG 81180
GGAGAATATT TAGGGGACAT ATTGTTAGTT GCTTCTCTAG TACTTTTCCC AGTAGACAGA 81240
TCTAGCATTT TTAACCTCAA TTGTGCATTA AAAAGCACCG AGGGAATTTA AAAGTAAATA 81300
CCAATCATAG GGACATTTGA ATTAGGATCT CAGGGAAGGG GCTCAGGAAA TCAGTAATTT 81360
TTAGAAACCC CACATGATTG TTATTGCTTA GGTAATAACA CCTACTGTCT ACCTTGTTGGT 81420
CCTGCCAAGG TGAAGTTCC TGGCCATGTT CCAGGCAACT GTAGTTCCAG GCTAGGGGGA 81480
GAACTGGACC ATGGAAGTGA GGCTCTGTCC AGGGTAGGGG AAGGGATGGA AGGTGACTGT 81540
TCCTGGCCAT GTTCCAGGCA ACTGTAGTTC CAGGCTAGGG GGAGAACTGG ACCATGGAAG 81600
TGAGGCTCTG TGCAGGGTAG GGAAGGGAT GGAAGGACTC AGTCTCTTGG GCCAAATCGG 81660

FIG. 6.31

TAAGGCAGCA TCTAAGCTCC TCTGAGAATA GGAAGGAGAG CAACCAATTG GAAAAAGAAT 81720
GGGAAACATG TAGATTCTCC TGCTTACCTT ACTTTCCAGT CTCAAAGCTG GAAGCCAGCA 81780
TTCAGTGTTT AGTTATTTTC AATGACAACA AGATTCAAAT CTTAGTTGT AAAGTTGTTA 81840
AAGGAAAGGA TTAGACTGAA AAGTTAAGAA GAACGGTAGA TGAAGAGTCC AAAGAGTTGA 81900
GGCTGGTCAT TTAACCATTG TGTGGCCACG CCCTCTCCAC AGGTGGAACA AGATGATCAG 81960
AATAGAAATG GCCAATTCTG ATGTGTTTCT ACAGTGTTC ACTGATTACA TTTTAAACA 82020
TCTGTAGCAA ACCATTTCCA TAATTTTTTT TTTTATTTT AGAGACGAGG TCTCGCTCTG 82080
TCACCCAGGC TGGTATGCAG CGGCATGATC ATAGCTCACT GCAGCCTCAA ATTCCTGGGC 82140
TCAAATGAGC CTCCTGCCTT AGCCTCCTAA GTAGCTTGA CTACAGGTGT GTAGCACCAC 82200
TCTCAGCTAA TTTATTTTCT TTTATTTTTT GTAGAGATAA TGCCTCGCTA TATTGGCCAG 82260
GATGGTCTCA AACGTTTATA GAACTGGTT TTAGGTTCTT AGAGGCTGGC AGCAATTCTC 82320
AGAGGTAACG CAAGCAGTCT TCCTGCCTTG GCCTCCAGT GTGCTGGGAT TACAAGGTGT 82380
GAGCCACCAC ACCTCATCAA TTTTGTGTTT AATATACTCT AAGGCTTATC ATAGTTCCGA 82440
GATCTTTTTT TTTTCTCTGA GAAATCTAGA AAGATGGAAG ACAGTATGGG TCTTTTGTGG 82500
ATTTTTGTCT CTAAGAAATT TTCATAAATG TCTGCCAAGG AAAAGGAAAG AGATCAAAGT 82560
GGTAATTAAT TCTTTAGGAT GGACATTTTT AGAAAAATGC TTTATAAACT TCCCCTCTCC 82620
CAACTCTGAG TGACTTATTG TGTCATACTG TATTAACACA TATTCATGCT GTAAATATAG 82680
TAAGAAAAGA CAATAGTTCA CAATTTTGGT TTAGTTTTTG CCATTATTGA TTATGAGCAG 82740
TAATCTTCC TTTCTTTTTT GAAGGTGATA TGGAAAGCCC TGTGTTTGCA TTTCCCTGCT 82800
TCTTAAACT AGAAACCCAC ATTGAAAAGC TCTTCTATA TTCTTTTTCT TGGGACTTTG 82860
AATGTTCTGA GTGTGGACAC CAATATCAA ACAGGTTAGT TTCTTTTGT TTTTAAATG 82920
GGTTCTTCTA GTTTCTCCAC CACTAAGGT AAGAGAACA TTTGAGCACC AGACACTACA 82980
GTTTGCTTGC TTCTTTAAAC TGAAGGGTC AAAACCTCAT CGTTTGATAG ACTGCTAGTA 83040
GGATATTTCC TAAGGAGTTC TTCAGTGGGA AATAGGGACG ATGAGAGGAA TAATACACCT 83100
CCCTCTCCA GAGTCCTTGC TGAGTAGAAT ACCTCTCAGA ATGCCATGAA ACTGTAGGCA 83160
TTTTGTGTTA TTCCTCTATT AGAAATGAGG GGTGTTGCTT GTTTACTTTA GGTGTTCTAAC 83220
ATTATAGACA CTAGTTTTAG GCTCTTGAG GCTAGCAGCA ATTCTCAGAG GTAATGCAAG 83280
CTTCCCCATT TCTCCCGTA GTCCTGTGAA AGACCAGCCA CCTCCAGAAG CCTACACATG 83340
AGTCTTCTCA GCCATACTTT CTGCTTTTCC TAATGCCTCT CAGCAGCGTA TTAGAAAGGC 83400
CATGATCGAT GTACCTGTTA CCTTCAGGCT TTGCATAAGG TGTATATGAA ACATAATGAA 83460
TTTCGTGTTT AGGCTCAGGT CCCATCCCCA GTTACCTCT TTATCTTGGA GACACTTCTG 83520
GTCCCATACA TTTAGATAA GAGATATTCA ACCTGTACCC ACCACGTAAG GAGAGGAATA 83580
GGTTTATGAA GAGGAGTCAG GGAGGCAAGG TATTCCAGA GGGATATTCT CACTTGGTCC 83640
ATACCTGAGA AAGTTGCTGG CTGGCAGTTA GGAAGATGAC CAGACTGGCT CAATTGTTCC 83700
TGTATCAAAA TTATTACAAT AGAAATAACT CTTTCCACCC CCCCCGCCC TTTTTTTTTT 83760
TTTGAGTTGG AGTCTCGCTC CCGTCACACA GGCTGGAGTG CAGCAGCGTG ATCCCGGCTC 83820
ACTGCAGCCT CCACCTCCTG GGTAAAGCG ATTCTCCTC CTCAGCTTCC TGAGTAGCTG 83880
GGATTACAGG TGTGTGCCAC CACGCCCGGC TGATTTTTGT ATTTTAGTA GAGACAGGGT 83940
TTTGCCATGT TGGCCAGGCT GGTCTTGAAC TCCTGACCTC AGGTGATCCA GCCACCTGAG 84000
CCTCCACAG TGCTGGGATT ACAGGTGTGA GCCACCATGC CTAGCCACAC TTTTCTTTAG 84060
CTTAAGTGCT TAAGTTAGAA AACTTGAAGT CTCTCTAAGT TACTCAAGTA AAATGTGAGA 84120
TAAAAATATT ACTTTTGAAG GCCGGGCACA GTGGCTCACA TCTGTAATCC CAGCACTTTG 84180
GTAGGCCGAG GCGGGTGGAT CACGAGGTCA GGAGTTTGAG ACCAGCCTGG CCAACATGGT 84240
GAAACGCTGT CTCTACTGAA AATACAAAAA TTAGCCGGGC ATGATGGCGG ACACCTGTAG 84300

FIG. 6.32

TCCCAGCTAC TCGGGAGGCT GAGGCAGGAG AATAACTTGA AACCCGAAGG TGGAGGTTGC 84360
AGTGAGCTGA GATTGCACCA CTGCACTCCA GCCTGGTCAA CAAGAATGAC ACTCCGTCTC 84420
AAAAAAATT AAAAAAATT ACTTAGATAT TCATTATCTA AATATGAAAT CCTTTTATAG 84480
TATTTAAGGA GTAGTCAAGG AGAGTTCAGT CTGGGAGGAT GCTCCAGGGA ATGCAGGCAA 84540
CAAAGGTTTT GTTTTTTTTT TAACTGGTTA ACTCAGATCT ACTAGAACAG GGTAAGGGAG 84600
GCCACAGAGT AGACACCATG AGCAAAGCTA ACCCTCCTGA GTTGAAAAAA TTATGGACGA 84660
GAAGTTATCA TTGAAATTAA CTGTTGGCAG ACATATCCAA AGAATATCGC AAGGATTTGG 84720
TCCCTTTATG CATCCTGAGA CAGATGAATG TGTGGAATGG CAGCTGGTGG GCAACAGAGC 84780
GATATTGGCA TGGTGGTGAT ACAGGGAAAT AGTTTCATCG TGTTAAAAGC CATGGAACAA 84840
AGATACATAA TGGCTGCTCT GCAGAAAAAT CCACGTCCCC TCTCCAAAGG GCCTGTTTTA 84900
CTCTGATGTA AAAATTGGGT CAGATAAATT TTCATATTAA GCTTTTTGTT GAGTAACTT 84960
TTGTAATAGT CCCCAAAAC CCCACTAGAA CAGGGTGAGA ATTAACGTTT TATTCATACC 85020
TAGGACTTAA ATAATTTAGT GTAAGCAAGT GAGTATGAGA ACACATCTGT TTCCAGTCTT 85080
CTATCATTGC TTTATATAAA TTCTCTGGTT TTCTCCTCAC AGTAACTCAG TGAGGAAGAT 85140
CCTAGTGTCC TCATTTGGCA CGTATGGATA TGACAGCTTG AAAGGGGTTA GATTGATTCC 85200
CAAGATGACA CACTGTAAGT GGCAGAGTCA GGAGACACAC TTAGGCTCTT CTGGCCTCTA 85260
AGACTTTCTT GCTCACTGTG GTATACTCCT TAATCACTAC CTGGGTTTTA AATAATATAA 85320
ATAACCTTGC TGATTAAAAT CAGCTTAATT GTAGCTTCTC TGAATCCAT ATCTTAGTTG 85380
TTTGACAGTT TTCGGTTGAG TGTCTTCTGT GTGTTAGGAA CTCAGGCACT GGAAATAGTG 85440
TATCTTTGCC AAATTTACTA ATTAGGTAGA GAGATAATAC ACGAACACAT AATAGAGGTC 85500
CAGTGACTTC GTAATTAATC TGATCTTTGG GCTGCTTAAC GTTAGCTTTG AATGCAAGAT 85560
GTTAAATGCG TTTTAGAGAT ATATAGCACA AACTGTGAGA GCTCAAGGGA GGAAGCCAC 85620
TAGCCGCTTT TGTGCTTTT TTTGTTTTT AAAAATAATC TTACTTTGTT CTAATAATAA 85680
AAGTAGTTAT AGAGGGAAAG CTAATGAA GTGACGTTTT CTAAATATG TTTAATATG 85740
TCATAACTTA AAACCTATTT CCACTTAATC TGAAGGAGAA CTGTCCAGCA AATTCCTTG 85800
TTTTTGTA GCTGTTTTTA GTGCCAGCAT AAGGGCTTTT TACTCAACTT GGAAAGTGTA 85860
ACCCAGAGTC AGTTAAAAAC ATAGTCTTCA GAGGCAGATC TCAGGTCTGT TATTTATCAC 85920
TGACTCTAT GTGTCACTTT CCCCATCTGT AAAATGGGGA TAAGAATAGC ACCTGCCTCT 85980
GAGAGTTGTT TGGAAGATGA GTGTCCAGTG CCATGCCCTT TGCACATAGT TTAAGTGTTT 86040
AGAAATGTCA GATGTCATGT GGAGAATTAA CACTTACTTG CTGAGACAGT CTCCTTTTTA 86100
TAACTAAAC AGTAGGAGCC TTTACATAAC AATTATCTTT GAAAATTTAA GAATTTAGCA 86160
GAAATCAGTG CATTTGTTGA TATCTTTATG TTGCTTTGCT TTTAAATGT TAACCTCCCT 86220
GACTACTGAT GTTTTTAACA GACAGTGCTT CCTCACAAGA TTTATAAGTA TTTGCTATTG 86280
TTTAGAAAGG AAGCTTGAT CTCTTAAGTA GCTGCTCTT AAATTACAAA TATTTTATT 86340
AAAGTGATG CAGTTGAGGT TTAGTGATCA TCTTTAAAGG TCATCTTTT AGATGGCGTT 86400
GCTCTCAAGT ATTCAGACTA AAGTGCAAT TTAGAACTTG TGTAACCTGT GAAAACAAAA 86460
TTTGTTTACA ATTAATGCTG TGTGTGTGTG TGTTTTTTTT TTAAGGATTA AAAAAAGTTA 86520
AGTTGTATGT ATTCCTGATT TTATGTTTGG AAACATCCCC TTTTCATTTT TGGTTGTCTG 86580
TAATGGCTAG CCAGTTTGAG TTATTTGAGT AAGGGGTGAG CTCTTAATAA ATTTGACAAC 86640
CTTAGAACAG TGGTTCTTCA CTAAGGGCTA TTTTTCCCC CTTGGGACAT TTGGCAACAT 86700
CTACAGACAA CTGGATGCCG TTAGTGGCAT CTGGTGAGGA GAGGCCAGGG ATGATGCTTA 86760
ACATCCTACA GTGCACAGGA CAGTGCTTCA CAGCAAAGAC TCTCTGGTGA AAAATGCAGT 86820
GATACCATTG AGGAACCCCTG TCTTTTTTTC TTGCTTCATC TCATAGTTGA AAGATATGGG 86880
AAATTAACAT GGAGCATCTT CACAGAGCTT CTTTACTAGA GGTAGGGAGG AACATTGCCA 86940

FIG. 6.33

TATTAACATG ATTTGGGGAA ATAAGAAAGT ATGAATCACG AAAAAGGGGA GGAATACTTT 87000
TAGACATTGG TTAAATTAA TGTAATGCA TTTAACGTTA ATGAATTTGT TATGTCATTT 87060
TTTTATAGGC ATATGAAGAG TCTGGTCACC TTTACAAATG TCATCCCTGA GTGGCACCCA 87120
CTTAATGCTG CCCATTTTGG TCCATGTAAC AATTGCAACA GTAAATCACA AATAAGAAAA 87180
ATGGTATTAG AAAAGTGAGT TAAAATTGTC TTATAATTTT TAGTACAAAA TGAAGGTGGA 87240
TTTACATTTT TCTTAATGTG TAGGATTGAA AATGGTGACA ACAACTTACC TTTCTGAAAT 87300
TTGAGTTAAC ATATATTTCT GGGTTGCCAG CTGCCTCGCT CTATCTGGCC AGTGAGCCCA 87360
CTGTACCGGT GAAGCCACTG AAAAGCCAACT TTAGGCTGAC TCTCTGGCCC CACTCTCCTA 87420
GTGTCTTTCC TTCTTTTTCG CTTTTTCTC CCTTTAAGGA TATCAAGCTT CAGTTTTTCT 87480
CTCCTCTGCC AAGTGTATGG AGTTTCTAGA ATTCTGGGAT TTCCTTAATC AGATTTCAAG 87540
AACTAAGATG ATCAAAGAT AAGCCACAGG CTCATCTCTC TGAATTTCCA TCTTCTCCTA 87600
GATCTCAGCA TGCTAATTCC TCATCATCTT GAAAGCTATC TAGTGGCCTT GAGCAGATAT 87660
ATTTTCATTG TATTTTGCCA GCTTTTCTGT TTGTCCTCAG TTGGGGAGGT TGGTCAGCAT 87720
TACCTTTTCC AGTATTACCA GAGAACCATC TGTTTAACT CACAGGTCAG TTCCATCTCA 87780
GGCCGTTTCC CTCTGTCTCA TTAATGCACT CACACATGTA CACAACCTCT CTACTCTTCA 87840
TTTTCAGTCT AATCGTACAT TAAGGAAATG TTTTGAGGTC TAATTTGATG TAATAAAGAA 87900
CCGGGAACAT TAACCTTTAT GCCCTTGAAT GTGCCAGAAA CCCTTCAGAA TCTTTCCTAA 87960
AGGTTTATTC TCATTGAAGT AATAAATCCT CAGTTTATCA GTGCTTACAG GCTCAAAGG 88020
GAAAAAGGGC AGTAGTCCCC TGTTCCCTCC TCCAGGTATC TACTTTAAAC CTTCAAATTA 88080
AGGTAGTATT TACTTTTACT TTTCAAATTG ATGTGCCTAT TCTACCGTAA TGCAGTCTGT 88140
TCTCCTTTTA TAGTAATTGA GACTAGGGT CTCACACCAA CACCTGGGCC CCATCTCTGT 88200
TTAGCCTTTC CCTGTCTTT CAATGCAATT GCGTATTTGG CTAAGTCAGT ACTCGGTGTT 88260
TGCATTGTTA TTAATATACA TGTGTTATTC CCTCTTCAGC CAAGCAGTAT ATATAGTTAG 88320
GTTTCACTTT TACAATTCTT ATTTTCCGG GAATTGTTAT TTGCCTTGT TTCAATTTGTT 88380
TTATTATGTA CTGTGAGTTT TTGCCAAATA CTTTAAAGAC TTATTAATAA ATTTTCAATA 88440
CTCAGATGCT TCACAGTTTT TACTCTGTT CCTCTCCCCT TTTTTCCTG GAACTCTTTC 88500
CTGCCACCTT TCACTCTTTG CTGCAGTCTG CGCTGGTTCC TCTCTGGGCC TGCAGCATAG 88560
GGTGCTCTTT ATTATGTACA CACTTCCAGT CACTATCGTA GTTTTATAGC CAAGGCCTCA 88620
TCCCCACATT CTATCACATC TGTTGCCCAT AAATATCCAG TCCTTTAGGG GTTCTCTGGG 88680
AAAAATAAGC TCTTCTTTGT CATCAACATA TGCCTCCGT AGTACTCATG TCTTCACTTT 88740
GCCCCGTTCT CTGGGTAAGG TGCCACTTCT CTGTTTGCTT TCTGTCTCT AAATATTTGA 88800
CTTCTTATTT GCTTATTTTC CTTTCTTTGT CCTTTTGGAC TCATATCTTT TTTGCCCTC 88860
ACTATTATTT GATAGCATTT GTGTAGGAGG GCGAAGTGGG AAGGAAGAGG AGGTGTCTGT 88920
ATCTGTCTGA AGATTACAGA AGTCTGTAAT CTGTCTTGGC TGCCAGGTGT CAGTTTTGAG 88980
ATGTAAATGT TGATGATGAG GTGAGGAGAA GAGCAGCAGA GCATGGGGTC TGCCATCCTG 89040
CCTTGACCA TGGCCTGCTT TAGGCTGCTT GGTGTATATG ATTCATCTA GCTGTTCTA 89100
CCTGCTTTTT CCTGTGCCCC AGCACTGAAC ATAGACTCGT ACCATTGTTT TGTGTAATCT 89160
GTTAATTGGT TGCCTGTCAG CATATATATT TTTTAACTAT ACAAATAAGT TGCTTCCCTT 89220
AAAGATTCAT GCTCTGATCT GGAAATGGAT TCATTAGGTA AAAGTCTTTT AATGGAAAAT 89280
GTGTTTTGAG TTCCAGTGGG CCAATTTATG AGCAGAATTT ATAATGTGGG CATTTCTGT 89340
TTTCTTCAA AGTAAATTGA ACTAGTGTAT GAAGTTTAC TTAATTTTA AATGCCAAGG 89400
TCTTATATA AGTCCTTTGT GTTTTTTAA TTTTGAAATT TGTATACTT GATTTGTTG 89460
TGTCTAATGG AATTTAGAAA TAAATTTAAT ATAGTTTTTA GGGCTAACCT AAAAGTAATT 89520
GGGTTTCATCA TGGTGTCTA TGTAATTAAC ACATATAGAA TCCTAAAAAC TAATTAAGTT 89580

FIG. 6.34

CCTTGGACAC CTTATCTCAC ATAACCCACA TCTCTAATGT CTCCCCATTG GGAAAAGAGT 89640
CCATTGATAA ATCAGGTGAA TTATGCCTAG CGGGCCCCAAA TCTGCTACTT TTCTTTAAGT 89700
TGTTTAGGAG TTACATTGAG ACCATGGTGA CATGGAGCAC CAAGAAGTTA GAATCAGATT 89760
TCATTTTACT TGACAACTC TTGAAAGGTC ACTGCCACAG TCTCTCTTGA GTGCAAGGCT 89820
ATGGCTATGC TTTGTAGCAC AGGGACGCGA TATTTCTCTG CTATCTTTGG GTAGCAGAGG 89880
TTAACACAGC TCCCTTGTGC TTTCTTTCTC TCTTTTCTAT TTTCTTTTCT TTTCTTAAGG 89940
ATAGATCTTT AAATAGGAGG AGTTTAACCC CATGTTAGGT GAATTCAAAT GGATCTTAGC 90000
CTGATGTCTC TTGTTCTCTT TTGGTTCAG TTTGGTTAAT TCCTTTCATC CAATTTTCCA 90060
GTGGTTGAGG GAGAACCTAA CTTGCTCTCC TCGACTCTGA GCATCATCCT TCACTGACAG 90120
TTCAGGCATT GTGGGTAGGA AGAAGTCTGA GAACAAAACC TAGGGATAAA GTTTAGTAGA 90180
GATGGGGTTT CACCATGTTG GCCAGGTTGG TCTCGAACTC CCGACCTCAG GTAATCCACC 90240
TGCTTTGGCC TCCCAAAGTG AGGCTGGAAA TAAGACATGC TGGAAATTGTA AGTAGGACAC 90300
TAGAGTCTAG GGGAATCAAA GAGGAAAATG AACAGAAAAG GGAAGGGGAA GGATATTATT 90360
TGATTGACTC CAAGATGCTA CTGTTTGTA GTTTTACCAT TTTAAAAATA TGCCATTAAG 90420
AAAGAAATGC TGGCCGGGCA TGGTGGCTTA TGCTGTAGT CCCAGCACTT TGGGAGGCTG 90480
AAGCGGACAG ATCACCTGAG ACTAGGAATT TGAGACCATC CTGGCCAACG TGGTGAAACC 90540
GCATCTCTAC TAAAAATACA AAAATCAGCT GGATATGGTG GCACATGCCT ATTGTCCCAG 90600
CTACTCAGGA GGCTGAGACA TTAGTACTGC TTGAACTGGG GAGGCAAAGG TTTCAGTGAG 90660
CAGAGATTGT GCCACTGCAC TCCAGCCTGG GCAACAGAGT GAGACTGTCT CAAAAAAAAA 90720
AAAAAAAAAGA AAGAAATGCT GCTTATTTAA CTGTGTTCTG TCAATGTTAA GGTGTATCCC 90780
GACTTCAGAG ATGTTAACAA ATGGGAAAAA ATTTGGAATT CATTAGGCAT TTGGAACCTA 90840
CAAAGTTTCG GCCGGGCATA GTGGCTCATG CCTGTAATCA CTTTGGGAGG CCAAGGCCGG 90900
TGGATTACCT AAGGTCAGGA GTTCGAGACC AATCTGGCCA ACATGGTGAA ACCCCATCTC 90960
TACTAAAAAT AAAAAATTA GCTGGGTGTG GTGGCATGCG CCTGTAGTCC CAGCTACTCA 91020
GGAGGCTAAG GCAGGAGAAT CGCTTGAACC CAGGGGGCGG AGGTTGCAGA GAGCTGAGAT 91080
CGTGCCCTGC ACTCCAACCT GGACAACAGA GTGAGACGCC ATCTCAAAAA CAAACAAACC 91140
AAAAAAAAAA AAAAAATTC ATAGTTACAG AAAGTAGTAT GGAGGCCATA CCGAGATTTT 91200
CGACATGGTA GTAAACTCT GCATTATGGC TCTGTTCTGC ATCATCTCTG TTCTGCATCG 91260
TTTCACTCCA CATCAGACCC TGGATAGCTT TGGTGTACTG GTCGATCTTG TGGCAGTAAG 91320
GCTAGTGTA TTAAGAGGAT ATTTTAAAC TTAACATATA ATTGCTCTAG TTGTTGTCTC 91380
TTTTTTGCTG GTTAAGAAAA TCAAATTTCT ATCCTATCTG AATCTCATAG CAGACTTTGG 91440
AGATTTCTGA CAAGTCATTT CTTACTACCT AGGGGAATGT ACTTGTAATC AGCTAGAGTC 91500
TGAGTATCTT CTACATCCAG GGAATTGGGC TGAGTGTGGA TTTTGGTCTT GGCAGTTTTT 91560
ACTTTTATTA ATTTGCAAAA GAATAGAAGA CTTGGAATGT ACAAGAAGCA TAAAAATGTG 91620
TCAGGTGGTT TTACATGCGT TATTTATCAC GTTAATATGT CTTAAGATAT TTTCCACGTG 91680
TAACTTATG TAAAGGCAGG AAAGTAGTGA GATTTTCATAT TCTAGGGATC AAGAGATTGT 91740
TTTAGTAAT AGCCTCAGAA AGTATCTTGA AAGGTATTAT ATAAGGTCAA GGAACATAAT 91800
ATTAGTAAAG AGTCAGGCCA GCGTGGTGG CTTATGCCTG TAATCCCAGC ACTTTGGGAG 91860
GCCAAGGCAG GCAGATCACT TGAAGTCAGC AGTTCGAGAC CAGCCTGGCC AACATGGTGA 91920
AACCCTGTCT TACTAAAAA TAGTAGTGTG TGGTATGGTG GCGCATGCCT GTAATCCAGC 91980
TCCTCAGGAG GCTGTGGTGG GAGAATCACT TGAGCCAGG AGGCGGAGAT TGCAGTAAGC 92040
TGAGATTGCA CCACTGCACT CCAACCTGGG TGACAGAGCT AGTGTCTGTC TCAAAAAAAG 92100
AAAAAAAAAA AGGTCAGATA GGTGCCTAAA GCCTGTGTGT CTCGCTATGA GAATACATCT 92160
CAAGTTTAC TGTGGTTCAT TGATTCAGAC ATGTAGTTCA CATTTTAACC TGTCTGAAAT 92220

FIG. 6.35

GGTAATATGT GAAATTGATG TCATGATATA GTTTAATTGG CAGCATGTTT TCATAGTGGT 92280
ACATTTTATA ATTAGTGAAA TCTTAGATTT GATGAAATAG ATATGATTTT TTAAGTGGG 92340
AAAGTTTAGT GTTATAGACA GTTTGCAGGA CTTTTATTT TGTAGGTACT TAAATTTTGA 92400
GGACTTAATT ATTCTCTAAT AAAGTGATTG ACAAGGATTA ATGTATAAAT TATACCTTGT 92460
CAGTCTGAAC AATCTGCAGT TTGGACATTG ATTCAAATTC ATTTAGGCTG AATAAATTTT 92520
GATAAACTAA GTAAGTTTTG ACAGCTATTT AAATATTGGG AAAGGGGATA TTCAACATTT 92580
TTCTTACATC CTGAGAGCTT TGTTAAATTT AGTTATTTGA GACCCATTGG GTTCTATTTT 92640
CTGGTTCAGC ATGTTGCTGT AATGGTAAAA TACAATTTTG AAATTATAGT TGTCTTGAAG 92700
TTAATAATAA ATTGACCAAT ATGTTGTATT TTTTCTCTA CTTAGTTACA AATTGAACTT 92760
TTCCTAAGTA GAACTTTTAA TTTGACAGGC CCCCTTTGCT TCCTGAGGTA ACTGAAATAG 92820
GCCAAATTAA TGCTTTTTTG AATATCTTAG GTTTGTTGCT TTCTTTCACA TGTTACCTAC 92880
CCCACTTAAC AAAAGCAATT AATCTCAGCA CTTGATGCCA AAGAAAATTC TAAAAGGTCT 92940
GGATTTTTTC CTTGGATTTT ACAAAGTAGC TACAATGGGA CTTTAAAGAC AAAGCTGCAT 93000
TGCTGCTTAC AGAGCAATTT TTGTTAATG GTCTGTGTTA GAGTCATACT GCATGATGAC 93060
TTCCAACGTG CTGGGATACC ATTCTGAAAA GGGTTTAGTG TTACATACTT CTTAGAGAGA 93120
GTTCTCCATT TCTAATTAAG GCACACATCT GGAGGTGCTC AAGAAAAATT AGTGCAGTTA 93180
GCCTTGGAAG TGTTATGTGT GACTAGTTCA CTTGAGACAT CTTTGTATA ATCAGACACA 93240
TGGCATTAAA TTTATTTAAC TTCTCTTGCT TTTCTCTCCC ACAGAGTATC TCCCATTTC 93300
ATGTTGCACT TTGTAGAAGG CTTACCACAG AATGACTTGC AGCACTATGC ATTTCAATTTT 93360
GAAGGCTGTC TTTATCAGAT AACTTCTGTA ATTCAGTATC GAGCAAATAA TCATTTTATA 93420
ACATGGATTT TAGATGCTGA TGGTAAGTGT TTAGAGGTTT TCTTTAAGA TAATTGGCAT 93480
AGAAACTAAA TTCTAGCATG TGGGGACTTT TTGGTTTTG TTTTATAAAA AAAGACAAAC 93540
TTTGTCTGA CTCTTTCTCT CTCCATTCTC GCCTTTGCCT TCTGCCCTC CTCGCATCTA 93600
TTAAAAGTGA TGGTTTTAGT ATCCTGTCTC ATTTTTCTT TCCCTTACAT CATGTATTAT 93660
AGGTAAACAC ATGCGCATGT GTGTATTTCT CTTTATAGACA AAGGATGAGA TTAATACTGT 93720
TAGCTCAGTT TTTTTTCCC TACTTAACAT CTTTGCTTTT ATTTTTTAGA CATATTTCTA 93780
AGACTATTAA ACATTAGACT TACGTAGCCC TTCTGTCATT GTGAAATACA TAGTTTACTA 93840
ACAGCTACCA TCAAGATAAA GCCTTTATTT AAATAATTAA ACTTCTTAGT GGAAAGCTAA 93900
GTAAGCACAG TTTATGGATT TTGGGAATTT TTGCCTTGCA TTTGTCTGAT ATGGTAAAT 93960
ATTGAGTTTG TTTTCTCAT AATGTTCACT TTGTCTTAGA CAAGATAACT CAATCCCCTT 94020
AAAGGGTTGT ATCAAGCCAT TGATAAGGGC TCACTTTGAT ATAACCATT TCTGTTATTT 94080
AGACACTCTT TCACACTTCC TATTTCTCTC CTGGGGATGG TTTGAATGGA TGACACAATA 94140
CCATATTATA AAAGCACTTT ACAAAGTGA ACTTATGTTA TAAATGTAAT TATTACCTTA 94200
AGGTTTTACC CTGTTTCAGA TTTGAGTGGA AGTAGTCTT TACAATACAA AACAATTAT 94260
TTTAATTTT TTTGCATTTT AAAGAATGAT CAATCCACTT CAGGTGCAGC ATGGTTTCCA 94320
ACCCTGACAG CATGGAAGAA TCATTTATTT AGCTTCTAAA AATGTGCAGG CTGTACCCTA 94380
GACCAGCCTT GGGGATTAGG CCCAAATATC AATGTTGGGT GTTTTTGGTA TTGGTTTTTG 94440
GCCCCCTAC CCGCCCTTCC TTCCTTCGTT CCTCTCTCTC ATTCTCTCTC TCTCTCTCTT 94500
TCTCTCTCTC CTTCTTTGCT CCTTCATTCC TTCTCTCTCT CTCTTTTTT TTTGAGACAG 94560
CATCTCACTA TATTGCCAG GCTGTTCTCA AACTCCTGGG CTCAAGTGAT CCTCCTGCCT 94620
CAGCTTCTG AGTAGCTAGG ACTACAGGCA CATGCTATGG CAATACTGTT TTAACATTG 94680
TTTTCAAGGC TCCCCAGGTG ATTCCAGTGT GGGTCATGTG GTAGAGAACC ACTGACACAG 94740
GCAAACAAAG GATACATAAA GTTGTCTATT TAATGGGTAG GTGCAGGTAG TAGATAAGAG 94800
TGTAGCCACA TAAACCACAT GCTTAGTGAA CGGTTTTGTT TTGTGTGTAT GTGAGGGATT 94860

FIG. 6.36

AGCATCTCTG AGTATATTTT GTTTTCCCTT TTGAACTTA TCAGAGAATT CATATGTCTG 94920
TTATGTGACT AATGCTCACA TTAAGAAAAG TTATGTGACT TTTTAAATT CATATGTCTT 94980
TTTAATTCAT TTATTCATTC ATATGTCTGT TATGTGACTA ATGCTCTCAT AAAAAAAGTA 95040
ATGCTCAGTT TACTTTTTTT ATATCAGATC ATATATATAT GTTTTTTTTT TTGAGATGGA 95100
GTTTTGCTCT TGTGCCCAG GCTGGAGTGT ATTGGCGCAG TCTTGTCTCA CCACCACGTC 95160
TGCTCCCGG GTTCAAGTGA TTCTCCTGCC TCATCCTCCT GAGTAGCCGG AATACACGCA 95220
GGCGCTACCA TGCCCGGCTA ATTTTGTATT TTTAGTAGAG ACAGGGTTTC TCCATGTTGG 95280
TCAGGTTGGT CTTGAACTCC CAACCTCAGG TGACCCACCC GCCTCGGCCT CCCGAAGTGC 95340
TGGGATTACA GGCATGAGCC ACCGCACCCG GCCATATCTT ATATTTTAAT AAATATTTTA 95400
ATTTGGTCTG TAAATTTTTT TTTTGGGGA ATGTGTTTTA AGTCTGTGTT GAGTCCTAGA 95460
CATTTGTTGT TCTCAGATAG TCACTAGTGA TACCTAACA TTAACCAGCC TGTTGGCAAC 95520
TAAATTGGCC TGAAGTGACA ACTAAGGAAA GGTCTCTTTC TCCTTTCTTA ATCTTTGCAT 95580
TCCTTAAGAT TAGTTCTTTG TAGGAAGGCT TTGAAGTCTG GTGGCAAGTA CCCTTTATCC 95640
CTCACAATCT TAAGATAAGG TCTTCTGAG CATTAAAAAG TGAAGTGGG AGATATGTCA 95700
AATGAGTTTT CTGTGTGTGC TCTGAGAAAT CTTTTTTTCA AAAAAGGATA GATGTACTTG 95760
TATAAGGAAA AGAGAACTG AGCGCACTTT CAATATTTAA GTAAGTGTCT CTAACATGTT 95820
TTGCAACATA AAATGATGAC CACTGTGTTG GTCATTACTT CTCTACTGCT AAAACAATGT 95880
TTTCTAAAAT AATATACTCC TTAGAAAAAA ATATAGTGCT TTGGGTGTGC ACTGTTGTAA 95940
TCCAAGGAAT AGGAAATGTT TTGTAGTAAG TGCGATGGTG TTTGACATCG TGATTTATTA 96000
ATTTATCACA TTTGGTTTCA TAGAAATAGA GTAAGCTACG TATTTGCTGT GCCGCAATTA 96060
CCATGACATT AACTTGTAT CTATTTCTGT TTCATAGATG TGTAGATATT GATATATACA 96120
GTGGAAGTAT GGATTGTTTT GATAAGTTTC TAATGAAAGT ACAGATATTT GTTGATTATT 96180
TATTAAGAAA GGTGTTACT CATCCAAGCC CGTGGTTAGC TTTTCCCAA TTATCATGTG 96240
GTAGTAAGTA AAATGTAAAG AAATATACCC TCCCTTAACC CCACACCACC TGTTAGCACC 96300
TAGCCACCTT CCTTACTTC TCAGCCGTAC TTTTGTATT TTTTGTGT AGTGGTAAAA 96360
TATAATAAC ATAAATTTA CCATTTAAC ATTTGTAAGT GTACAATTCA TTGGCATTGA 96420
ATACATTGTG TGCAACCACC ATCACCATCA GGACTTTTTT ATCAACCCAA ACAGAACTA 96480
CTCATTAAAC AATACTCCG CATCCTTCCA CCCCAAAGCC CTGGTAACCA CTATTCTACT 96540
TTCTGTCTCT GTGAATCTGT CTATTCTAGA TACCTCATAG AAGTGGAATC GTACATTATT 96600
TGTCTTTTGT TGTCTGGCTT ATTTTACTCA GCATATTTTC AAGATTCATT TGTGTTGTGG 96660
GATGTAGCAG AATGTCATTC CTTTCTAAGG CTGAGTAGCA TTGTATGTAT TATCCATTTA 96720
TCTGTTACGG ACATTTGACT ATTGTGAATA ATGCTGTTGT GAACATTGGT GGACAAGGAA 96780
CTGAAAGTCC CTGCTTTTCA TTCTTTTGG CATAAACCTA CAAGAGGAAT TGCTGGGTCT 96840
TAACGGTAAT TCTGTGTTA ATTTTGGAC GAACTGCCAG ACTGTTTCCA CAGCAGTTGT 96900
ACTATTTTAC ATCCCCACCA GCGTTACACA AGGATTCCAA TTTCTCTACA TCCTTGCCAA 96960
CATTTGCTAT TTTCTATTTT TTTTAATAA TATCCATCCT AATGGGTGTC TTTTTTTTTT 97020
TTTAAAGGAA TGGTTTAAAC AGGTTACCTT CTTACTCCTC ATTCATGCTT TAGTTGACTA 97080
CATAAGGACC CCTCTCCCTA TTGGCACCAT TGAAATTGTT CAGGCAAAAA TAACTGCCAG 97140
CGACACACTG CTTAAGTAA TGGACTTTTC CCAAGTTTGT TATTAATATT TCAGTATTTG 97200
GTAGTGCATC CTAAGTCTAG TTTTAAACT CTCCCTTGT CATCTATCAT CTCATTCTCT 97260
CTTGACAAAT GTGAAATGG AAGCTCAGAA ATAAACAAG AATTAAACG AATAGTGATC 97320
CTTCAGGTAA CAAGCTTCAT TTATCATGAA AACATATATG TATGAAACAT TCTGTTTTCT 97380
GATGTTATTG GATAAATTAG GTGATAACCA AATTCTAAGT TCCAAAAATT AAATATACTC 97440
TATCTAAGGA CTTTAACATG GCAGACAATG GTGACAAGGT CAAGAACATG TTTTAGAGTC 97500

FIG. 6.37

TTCTCCTTTG GTCGGTATTC AATGATACAA CAGTTGAAAA GGCCAGAAGA AAGTTAACCT 97560
AGGATGGTGG TTTTGAATA TCTAACTTTC ACTTCTTCC CATCTTCCAG GAAGTTGGCT 97620
GGAATGTGAT GACTTAAAAAG GCCCATGTTC TGAAAGGCAC AAGAAATTTG AAGTTCCTGC 97680
TTCAGAGATA CATATTGTTA TTTGGGAAAG AAAAATATCC CAAGTGACAG ATAAAGAAGC 97740
TGCCTGCCTT CCACTTAAAA AGACTAATGA CCAACACGCT CTCAGTAATG AGAAACCAGT 97800
ATCTTTAACA TCGTGTCTCG TGGGTGATGC TGCCTCAGCT GAAACAGCCT CAGTAACTCA 97860
CCCTAAAGAT ATATCAGTTG CCCCTCGTAC TCTTTCACAG GACACAGCTG TAACTCATGG 97920
AGATCATTTA CTTTCAGGTC CAAAAGGTTT GGTTGACAAT ATTTTACCTC TGACACTTGA 97980
AGAAACTATC CAGAAAACAG CCTCAGTTTC ACAGTTAAAT TCTGAAGCTT TCCTGTTAGA 98040
AAATAAACCT GTAGCAGAAA ATACAGGAAT TCTCAAAACC AATACTTTGC TATCACAAGA 98100
ATCACTAATG GCTTCTTCAG TATCAGCTCC ATGTAATGAA AAGCTTATTC AAGACCAATT 98160
TGTGGACATA AGTTTTCCAT CCCAAGTTGT AAATACAAAC ATGCAGTCAG TACAGCTGAA 98220
TACAGAAGAT ACTGTAAATA CTAAATCTGT GAATAATACT GATGCTACTG GTCTTATACA 98280
GGGAGTGAAG TCAGTAGAAA TTGAGAAGGA CGCTCAGTTA AAACAATTCC TTACACCAAA 98340
AACTGAACAA TTAACCAG AACGTGTCAC ATCTCAGGTA TCTAATTTGA AGAAAAAAGA 98400
AACTACAGCA GATTCTCAAA CCACAACATC TAAGTCATTA CAGAATCAGT CTCTGAAAGA 98460
AAATCAGAAG AAGCCATTTG TGGGAAGTTG GGTTAAAGGC TTAATAAGCA GGGGTGCTTC 98520
TTTTATGCCA CTCTGTGTTT CAGCTCATAA TAGAAACACT ATAAGTATT TACAACCTTC 98580
AGTTAAAGGG GTAAATAATT TTGGTGGCTT TAAACTAAA GGTATAAACC AGAAGGCCAG 98640
CCACGTATCC AAGAAAGCTC GTAAGAGTGC AAGTAAGCCT CCTCCCATCA GTAAGCCACC 98700
AGCAGGCCCT CCATCGTCTA ATGGCACAGC TGCCACCCA CATGCTCATG CTGCTTCAGA 98760
AGTTTTGGAA AAGTCTGGAA GCACCTCATG TGGAGCTCAA CTCAACCACA GTTCTTATGG 98820
GAATGGTATT TCTTCAGCAA ACCATGAAGA CTTGGTGGAA GGTGAGATT ATAACTTCG 98880
TCTAAACTT CGTAAAAAGC TAAAGGCAGA AAAGAAGAAA TTAGCTGCTC TTATGTCTTC 98940
CCCGCAAAGC AGAACAGTTC GAAGTGAAAA TCTAGAACAG GTGCCCCAGG ATGGGTCTCC 99000
AAATGATTGT GAATCAATAG AGGACTTGT AAATGAGCTA CCATATCCAA TTGATATTGC 99060
CAGTGAGTCT GCATGCACCA CTGTTCTGG TGTTCCTG TACAGTAGTC AACTCATGA 99120
AGAAATTTTA GCGGAATTAT TGTCTCCTAC ACCTGTTTCA ACAGAGCTGT CAGAAAATGG 99180
GGAAGGTGAC TTAGGTATT TGGGAATGGG AGATAGTCAT ATCCCACCAC CAGTACCAAG 99240
TGAATTCAAT GATGTTTCCC AGAACACACA TCTGAGACAG GACCATAATT ATTGTAGCCC 99300
CACCAAGAAA AATCCATGTG AAGTTCAGCC AGACTCTCTG ACAAATAATG CCTGCGTTAG 99360
AACATTAAAC TTGGAGAGTC CGATGAAGAC TGATATTTTC GATGAGTTTT TTTCTCCTC 99420
AGCATTAAT GCTTTAGCAA ATGACACATT AGACCTACCT CATTCGATG AATATCTGTT 99480
TGAGAATTAT TGAATTAATG CTTGTAACT TTTTTCATAT AATATTTATT ATTATTAGAA 99540
GAACTTACAA TGTGTTCCAG TAGTGTAT AACTGGACT TGTGTAATTA CTTGTGTAAT 99600
AACCATGAAC AAAATGCAAG GTTTAACCTT TGGTCTGCCC CATGAAGCAT GTAATCTTTC 99660
TTACACATTA AAATCACTGA ATGTGTTCTC CTTTTGGTT TCATTTTGTT CTTGTGAGAG 99720
TATGAGGATT TCAAAATGTT AAAGATGAAA AGTGGCGTCT AGTTTCTGAC AGTTTGTACA 99780
GTTGGATGCA TTACATTTT AGATTTGAAG TTTTGGTTAT GTTAGTGTTA TGAGTGATCT 99840
TTGTGGTGGT TTTCTTCCCC TGGAACCTG TTGCTCGTGG CGCTTGCCC ACGGTGCCCC 99900
AGTTCTTGTC CTGTGTCCAG ATATGCAGAC AAATGAAGGG TGAAGAAGAA GAAGAGGAGC 99960
TTTATTTAGT GTTAGAACAG CTCAGAAGGA GACCCACAGT GAGCAGCTCC CCTGTGTCCG 100020
CGGGCAGGTC GTCCCTCAAG TGTTAGCTC TCAGCAGAGA AAAGGCCCTG GAGAGGGTGA 100080
CTCCTCTCAG CTCTCAGCAG AGAAGCAGCC CTGGAGAAGG TAGCTTCTGT TCGCAGGCAG 100140

FIG. 6.38

ATTGTCCAGA GGTCTGCTG CTCTCAGACG GGGCCCTGGA GAGGATAGCT TCTATCCATA 100200
GGCAGGTTGT TCTGCCGTCT CTACAGGTCT CTGAAGCTCT TAGCAGAGAG GGTAGCTCCT 100260
CCCTGTTGCT GGTCGTCCCA CCCTCTGCTC AGTTCTGGCT GAGCCTGGGG CATTTTACGG 100320
GCCTCGGGGG AGGAAGTGCA TACTTACTGG CCTGAAAAAG GCACCAGTTC CCACTCCTAC 100380
AGGTGGGACT GGCAGCCTGG CCCTCAGCCT TCAGGCCCTC CCTGTTTATG GCTTCCAGGC 100440
TTACCCCCCT GCTTTGATCT GAGAGCTGGT GCCAATAGCA GGGAGAAGCC AAGCTGCAGA 100500
GGCAAGCACT TCCGAGCCTG CAAAAGCAGG CCCCCAAAAG TGCAGGGATG CCTGAGTCTG 100560
CACCCGCACC CAGGAGGGTG GAGATCTTGC CTGCTCCAAG GCTGCAGCCG GAATGATAGC 100620
AGGCTGACTG GAGCACCTGC CACCATCATT AGTTCAAGAG TTTATGCAGA TTTAAGTTGT 100680
ATACGGTATA TGAATGTGTG ACAGTTTTCC TTATGGTTGT GTGGCCTTCT GTAAGAGCCT 100740
ACGCCTGTTT GTTACACCGG TAGAGTGCTG TGGAATGTAA ACTTTCCCTA TGCTACTTAT 100800
CTCCTTTATC TCTCCATACA GAGGAGGGCA AGAAACCTTG TTAAGTGAAC TTTAGTAATG 100860
TTAAGTGATC AATAAATCTA TAAATAATG ATAGCAGAAA AAAGTTACCT GTTTTTGTGA 100920
TGATGTACAA ACTTTACATG TTATCACAAA TACCATCTTT CTTCCCAAGA CATTACTTC 100980
TGTAACCAAA GTGGGACACC ATCTAACAGT TCTGTTTTGG GAGAGAGTAA TAACCAGTGC 101040
TTGTGAGGCT TGTTAGATGT TGGTTGTGAT ATATGAGATA GATGTTATTT CATTAGACC 101100
TCAACATTCC TGTGCGTGAG ATACTTTTAT CACATCTTAC AGATAAGGAG ACTGTACTCA 101160
TTCAGTTGTG GAGCTGAGAT TGAGTAGAGT GGCTATTACA GCAGTTGAGT GCTGAGCTTA 101220
TCAATATATG TTCCACTCCT CAGGCTTCAT TTAAGTAGG ATGCCCAAAC AGCACCCTG 101280
CCGTAGAGAT TTGAGTTAAC AGCAGTACTT ACTGAGGTTT AAGGCTGGCA GCCAGTGTCC 101340
TTGCAGTAAA ATTATTTGCT AGGGACTCAG TACTTCATAA TCTATTTGTC AGATTTACTC 101400
CTAAGCTTCT GTGTTGTTTT ATTTTTTTTC TGACAAAAGT AGTGCATATT GTCAAGGAAA 101460
AACTAGGAAA ATACCAAAAA AAAAGATTTT TGACCATGCA TTTAATACT TAGTGACTAC 101520
AAACATTTTC CTATTTTATG CATATAGATT TAAATAAAC GTGAGATCCT ATTGTATCTG 101580
TTTTAATGGA TAAACATTGT TCACTGTTT TAAGATTCTG AGGTGATTTA TACTGTCTTG 101640
CCATTGTAA TTGCAGCAGT TAGCCTTGTT GATAAATTTT TGCATGGATC CAAGTTTTGT 101700
TTTCCAGGAG TGGAGTTGCT TGGTCAAAGG AAATGCACAT TTAAGGTTTT TTGGTGATTG 101760
CATGACTGAC TTCCCTGGG CCTCGCCAAC ACTAGGTAGT AGTATTGGGA GGAAGGGGGG 101820
AACCAATCCT GGGTGCTCCA AGATTACTAG TGAGCCTGAA CATTCTCTAT AACTATTGTC 101880
CACTTGAGTT GTTGTTTTGT TTTTTTTTTG GTGGAGGCGG GGGTGGGTTT AAGAATTGCT 101940
TATCCTTTC TGTACTAAT TATCTTTTCA ACAAATATTT CTAGATTACT GCTAAGGACC 102000
AAGCACTGTT ATCAGCCTGA GATAAGGCAG CACACTAGAA GGAAATCCTT GCTCCTTTTG 102060
AGTTTGCTT CCAAACATGG AGATCAATAT ATAATGTTAG GTAGTAATAG GAGATACATG 102120
CAGTTGATTG ATGTCATTTG TAGTAGTTAT GGTCAATAAA GTTGCCTTGA AACTGAATT 102180
AGTATAAACT GAAATACTGT TCCTAGGGGA AATAGGTTCC TGCTAGCCTG TGGTCATGAG 102240
ATTTTGTCA AACAATCACT ATATAACCTT TTCTGTTTCT GTTTAAAGAC ATGTTATTTG 102300
ATCTATATGG TTGATTCTTT ACATTAACAT GGCCAACAGC ACTGTAACCTC AGCCTGAACG 102360
AAGCTTATCT GACACATGGT GTTCTCCATA AGGCACATCA TAGCTTTCTG TGCTTAGGAA 102420
CACTAGACGG CACTTCAGCA CTGCACTTGA GGACGTTTTA AACAGTGAAA TCAACAAAAA 102480
GCACAAAAAA ATGCAACAAT AGGCTGGGCA AGGTGGCTCA CGCCTGTAAT CCCATCACTT 102540
AGGGAGGCCG AGGCGGGCGG ATCACGAGGT CAGGAGATCA AGACCATCCT GGCTAACACG 102600
GTGAAACCCC GTCTCTACTA AAAATACAAA GAATTAGCCG GGCGAGGTGG CAGGCGCCTG 102660
TAGTCCAGC TACTCGGGAG GCTGAGGCAA GAGAATGGTG TGAACCTGGG AGGCGGAGCT 102720
TGAAGTGAGC CGAGATTGCG CCACTGCACT CCAGCCTGGG CGACAGAGCG AGACTGCGTC 102780

FIG. 6.39

TCAAAAAAAAA AAAAAAAGGA ACAATAACAA AGACACTAGT CCCCCAAAAA TACACTTGTT 102840
TACAGTGTGA ACTGAAAGAG GAAGGTGGAG TATTGACTTG TTTGACCTCA GCTGGAAATG 102900
TGCACGTCTT GTGACTCAAA TTTTCTCTG TTCTGTGCAT GCATGTCCAC GAATAACCAC 102960
AAGAAGCACT GAAAGCATTG ATTTTATAGG TTACAAATTA ATTTTAGCAA GTAAATGAAT 103020
TCACAAATAC GGAATCTGTG AGTAATGAGG ACTGATTCTT TTTTTTTTTG GAGATGGAGT 103080
TTCACTCTTG TAGCCTAGGC TGGAGTGCAA TGGCATGATC TCGGCTCACT GCAACCTCCG 103140
CCTCCCGGGT TCAGCCTCCA CCTCCCGGGT TCAAGCGATT CTCCTGCCTC AGCCTCCCGA 103200
ATAGCTGGGA TTACAGGCTT GCACCACCAT GCCCGGCTAA TTTTGTATT TTTAGTACAG 103260
ACGGGGTTTC ACCATGTTGG CCAGGCTAGC CTCGAACTCC TGACCTCAGG CAATCCACCC 103320
ACCTCAGCCT CTCAAAGTGC TGGGATTACA GCGTGAGCC ACCGCGCCCG GCCGAGGACT 103380
GATTCTTATG TCAGATGGCA CTAAATGCTA TGGAGAAGAG GAGTGGATGA GAGGGAGAAG 103440
TATTTTAGAC CAGGTAGACT TGGAAGGTTT CTTGGAGGTG GGTGATGTTT GAGAAGAGGC 103500
TTCAATAAAG TTAGGGAGCT CGCCATGTGA TTGCAGGAAG AGCGTTCCAG GAGAACAAAA 103560
GTCATGAAGA GTGAGTGCTA GGCATGTGTC TGGTCTGTTT GGGCTGCTAT AACAAAATAC 103620
CTTAGACTGG GTAAATGTA TAAATAATAG AAGTGTATTG CTTATAGTTC TAGAAGCTGG 103680
GAAGTCCAAG ATCAAGGTAT CAGCACATTC TGGTGAAAGC TGCTCTGCTT CATGGCTGGT 103740
TCTCTCACTG TCCTCACATG GCATAAGAGG GGCACAGAGC CCTCAACCGT CTCTCCAGTG 103800
GCCCCATCTC TTAGTACTGT TGGATTGGGG ATTTAGACTT CACTAATTTT GGGGGGACAC 103860
AAACATTGAG ACCACAGCAG CATGACTGAG GATAAGCAAG AGGCCAGTGT GGTTGAGCAG 103920
AGTGATCAGT GAAGGAGAGT TAGGACATGA GTAAAGAGGC TAGCAGACAC CAGATCTCAT 103980
ATGGCTTTGT AGGCCATAGT GAGGACTTTG TTTAAGCTGA GAATAATAGA TAACCTCAGG 104040
AAAGTTTCAG GCAAGAGGGT AACATGATCT GATCTGGGT TTTAAAGGAT CACTGAAGTG 104100
GGGAGACTGT CTACAGATGG TCTGAATAGG AGTCCTAGTC TATTACAATC TCCTTGGAGT 104160
TTAGGGTGGT AACTGGAGGT GTTCAAGAGT AGTTGGATTA CTGTTGGATT TCAAAAGTAG 104220
AGCCAACACG ATATGTGCAT TGGCTGTGAG GTAGAAGAGG AGTCAAAATG AACTCCAGGT 104280
TTTATTGACT GAGCAATTGT GCCATTTCTT GAGATGGGTC AGATTTGGGA AGGAAAGAAT 104340
TTAAAGGGGA TAAGATAATC CCATTAGGAG TGTGTTAAGT GTGAGATTCC TATTAGACTT 104400
TCGAGTGGAG ATGATTTAAT AGGAAGATAG ATCTGCAACA CTGGAGCTCA GCGGAGAGGG 104460
ACACCCTGGA GATAGCCGTT TGGGAATTAG GAATGTGTGG ATCATGTTAT AGGATGGGGT 104520
CATTTAGGGA CTTAAACAG CTCTGAAGAA CAAAATGGT GCCTTGATCT TGGACTTCCT 104580
GGTTTATAGA ACTGTGAGCA ATATATATAT ATTTTTC AAGACAGAGTC TTGCTCCGTC 104640
ATCCAGGCTG GAGTGCAGTC GCACCATCTC GGCTCACTGC AACCTCCACT TCCTGGTTCA 104700
AGCAATTCTG GTGCCTAAGC CTCCCAAGTG GTTGGGACTA TAGGTGTATG ACACCATGCC 104760
CGACTAATTT TTGTATTTT TTGTAGAGAC AGGGTTTTGC CATGTTGGCC AGGCTGGTCT 104820
CAAACCTCTG ACCTCAAGTG ATCTGCCTGC CTTGGCCTCC CAAAGTGCTT GGATTATAGG 104880
CGTGAGCCAC CATGCCCAGA CTAATTTCT AACATTTATA AATTATCCAG TCTAAGATAT 104940
TTTGTGATAG CAGCCCAAGC AGACCAAGGC AAAGGCCAAG CACACTTGCT CCTCCTGACT 105000
TTTGCTCTTC CTGGAATGTT CTTCTTTAG TCACATGGTT GCCTGCCTAG CTTCAATCAA 105060
TAGGAGTGTG GTGCCCTGAA AATACAAGGA AGAATGCTTT TCTTTTTTTT AAAAGGAAGG 105120
GATGATTATC TGTCAGATGC TGCTGAAAAA GAGTAATAGA GTAATTGGCC ACTGGCTCTG 105180
GCAATAGGGA AGTTAGCTCT GCTAACTCCA CATGAACAGT TTCACATGAA CAAGTGTGAG 105240
TGGGCTCAAG AGAAGGGATG GTGAGAAAGT GGAGCTATGG ACTCACTCTT GAAACATTTT 105300
CTGGTGCTC GTAGGGCAAT GTGAGGTCAA GGTTTTTGTT ACTGTTCTGA AGATGGGAGA 105360
GGCTGACACA TGGATGTTGT AGGTGAGAGA AGGGGCGCTT GCGGGGCAA ACTTCTCCAG 105420

FIG. 6.40

GGATGGGATT CCAGTGTCTA AGAGGAGGCG GTGTGACCCT AAGAGCTAGA AAAATTATTT 105480
TATTAATAGG AAAGACAAAG TACTTAGGCT CAGATGCTAA GAGATTTGCT GATAAAAGAA 105540
TGAGAACGGT CTCTTCTGAT TATTTTCTTG GGGAAATAAA TAGATCATCA GCTGAGGGTG 105600
TGAGGGGAGA AGGAGTTGAA CATGGAGGAA GACAGGTGTG AAATATTGGT CTCAGAATGG 105660
AGAGCGAATT GAATAGGGAC ATGCAGTGGG CTTGCTAAGC TGTGCGGAGA GCCCGTGGGA 105720
AGTTTATGGT CATCAATTTA ATGGCGACCA GCCAAGATGG TGGTTTATTT TTCTCCAGTT 105780
GTATTTAACT GCTCAGGTGC AGGACAGAGA GACTAAGTGT GAAGTTAATT TCAGCCAACG 105840
TAGAGGAATT GTCAGGCAGA TGGGACAAGG AGATAGAGGA GAAAAGGAAT AAGGCTTCCT 105900
GCAAGGGTAA TGATTGTAGG GATGGATAAG TAAGGAACAC AGGAAGTGGC TGTCTGCTGA 105960
GTGGTGCCAG AGCTCAGTGG GTCAGAGCAA GGTTCAAAGA ATGGCAGAGA GGCACCTGTG 106020
GAGGAAGTAA GCTGGCTAGA AAGTAGTGTG CTTGAAATTA AGCTTCTGGA GATAGCAAGG 106080
TTACAGGTGA TGACAAAGTC TGAGTATGAC AAGGAACTG CAGGGCCAGA GTTGGCAAGA 106140
ATTCATGAAA AATGAGGAGA AAGAGGCACC AAGAGGCTGG GATAGCACAT GGATTGTCTC 106200
TGTGTGAGGC AAAGTCATCT AAATGGCAGC AGTGGCCCTA GCAGAAAGAA ATATACAGTG 106260
AGCCGGAGCA AAAATCCTCA AGGACAGGCA GAACGCCATG AAAACGGCAG ATGACAGCCA 106320
AAGGAGCAGG GGCAGGGGGCT CAGTCCAAAG TGTTTCAGAG TCACTGGAGG GTTGAGTGGG 106380
AAGGGGAGGG AGTGGCTGAA ATGGCAACAA GGAAGAACCT CTCTCATCTC CAGGCCCAAA 106440
AGTATGTGGA ATGCGGGAGA TAAGACAGCC ACCACTGGCC AGGGCTGTAA AGGGACATTC 106500
AGCGAATATT CAGGTTCCAT TTAGCACGAC AGCAGGGAAG GGAAGTGTGG CAGAAAAAAA 106560
CTGGGGCAGT GGGATTAAAG ACAGACCACA CATTCCAAAA GGCACCGTGG GAGGGTCAGG 106620
GGGCGAGGTT AGGTCTAGGC TTCAGTGTCC TGGGAGACTC AGTCTTCACA GGGTGACAGC 106680
GATCAAGAGT GCAGCTTAGG CTGGGTGCAG TGGCTCATGC CTGTAGTCCC AGCACTTTGG 106740
GAGGCCGAGA CGGGAGGATT GCTTGAAGCC AGGAGTTTGA GACCAGTCTG ACCAACATGG 106800
CAAAACCCCA TCTCTACTAA AAATACAAAA ATCAACTGGG CATGGTGGCG TGTGCCTGTA 106860
GTCCAGCTA CTTGAGAGGC TGAGGCAAGA GAATCACTTG AACCTGGGAA GCAGAGGTTG 106920
CAGTGAGCTG AGATCGTGCC ACTGCACTCC AACCTGGGCA ACAGAGTGAG ACCCTGTCTC 106980
AAAAACAACA ACAACAAAAA AGAAAAGAGT ACAACTTATG AAGGGGTCTC CTGGGGAGAG 107040
GGTTTTTGGG ATTCTCCTGC CTCTCAAAGT GCTGGGATTA TGGGCGTGAG CCACCACACC 107100
CAGCCGAGGG AGGCTGAGTT CTAATTGTTG TATCTCTCTT GGGATTGGCC TCCTGGGCAG 107160
TTTAAAAGAC AAGGCAAGGA ATCTTTTGGG GAAAGAGACT GGGGGCAAGG TGTGTCTGAA 107220
CAAGAAGTGT GAGAAGCTCT GTGGGCTCCC TTCAGACTTC CAGTCGTTGA ATTGGGATCT 107280
CATTTATATC AGCTCTAGGT GTAACGATAT TAAATCTTCT CTGTCATTTG GCAATTTTGG 107340
TTTATGCTTG ATCATCATTT TTAATGTTTC GACATGTAGA AGTTTAACAT TATTTTACAT 107400
TCTTTTCCTT CTGGCATCAT GTTTTAGCAA GATTGTTTCC ACCAAAAGAA TATATATATC 107460
TTCTAATGAA ACTACGTTTC TTTTTTTTTT TTCTTTGCT TTCTCTTTTG GTATATGAAT 107520
CTTTGATTAT TTGTAATGTA TTTTGATGTG TAACACTGAA GTTTCTATTT TGTACTATTT 107580
TTTTCCCAA ACAGTAAACT TATTGTTCAA ATACTTATTG AACAACTTC ACTATTCTTT 107640
AACCATTTAG AATACGCCAT TCACATATCT TTCATACTAC ATTTAATAAC ATTTTTTAAT 107700
TAAAAAATAT TCTACTGATT TGTTTATTTT GAGACCAGGT TATGAACTG GCTAATTTTT 107760
GTATTTTGT TAAATACCGA AATCACTGT GTTGCCAAGG CTGGTCTCGA ACTCCTGGGC 107820
TCAAGCAATC TGCCACCTT GGCGTCTCAA AGTGCTGGGA TTACAGGTGT GAGCCGCTAC 107880
ACCCGGCCAC ACCCGGCCAA CACATATTAT TTGTTATTAC ATTTAATTCC CACAGTACAT 107940
TGAAATTATC AGGGAAAAGT TTTCAGTGAA ACATTATTGA ACGCCACATT AAAAGTGTA 108000
ATTACAAAGA TTTAATGCCA ATTTTTCAGA AGAAAAAGA CCAGGAGGAA GGTCTATGAA 108060

FIG. 6.41

GTTTTAGCCA GTCTCTCATC CACCTACCAT TTCACGATCA TGCACGTGT AAGTCAGGAA 108120
AAGAGTAAGA AAAGTGAAAG ATACAATTGA TTAGAGAGTT TTGCTGGATA CTATAGATGA 108180
AAAGAACACA AAATGGAACA GCCTCTTCAA GCTTAGAGTC AACGGCTGTA GTCCCAAAGA 108240
CTGTAGTCAG AGGCGGTAGG GCCAAAAGAC ATGACTTATG GCATTGGAGG AAGAGGATGC 108300
TTTGGGAGTT CATGGTAGAA GAGGCGGAAA AAATCTGGTG GATTAAAGAA AGCATCCCAA 108360
AGTGACATTA AACTAATGAC TAAATTCTGA GCTGTTTTCA GGGGCAAAGC CTGTTTGGGC 108420
ACCCCTGCCA CACTTAAAGA GTCACCTAGG TATGGTTCGT GGGCTCTGAA CAGGCCTGCT 108480
CAGTGAACAT ATTTGTGACT GTTCTCCGG CCCTTTTAGC TGTATTGAGT AAAATTTAA 108540
GAGACCATTG TTTTGGCCTA AGCTCCTGCC CTAGGCCCAA AGAACAGACC AAACCTGAAT 108600
GGCTTCACTT GTCCTAGGTG CTGTGTACTC AAACCTGAAT TTGAAACAGG TCGGTTTTTC 108660
AAAAAAGCA AAAGATTCAC AGCAACCAAT TAGAAGAGGC CCGGTCAACC TGAGCCAGCA 108720
TGATGAGGCT CTTCTGCTTT AATCCTACAA GGAAAGAAAC TTTGAAATGA CCAATCTGCT 108780
TTCATTCTTG GTTCTGCTT TCTTTGGTCT ATTTCTGCCT GTAAACCTA TCTCCTCTGC 108840
TCAGCTCATT GAAGTACCCT TCTATTTATA GATGGGATGC TGCCCGACTC ATGTATCGCT 108900
AGTAAAAGCC AATTAAATTA TTACACTCGA TTTGTTGGAA TTTTGCTATT TTGACAGCTT 108960
TTCAAAAACA CCAGTAGGTT CACATCCCTA ATCCCCAGC CAGTGTCCC TCAAGGAACC 109020
ATGGAAGAAG CAAAGGTGGC TGAAAGGCGC CTCAGGATGC TTCTAAGCAC GGCACATCCA 109080
TGAAAGGCA CTTACTAATA TTTGCAGGAT AGCAAAGCAC TGCAGTGACG ATAAATCTAG 109140
TATTGGAGAA GTTCAAAATA ATCAGTAGAT TAACACAGAA GCCAGAGCTT ATAGGGAGAA 109200
AAGGAACCCT ATGAAATACT TCAAATCCGA AAACGAACAT GCATTTCTG TTAGTTAGT 109260
GCAGGTACGT AAAAGCTTGG TAAAGTACCC TTCTTGCCAG CTTTCTCTT CTTACAAGCC 109320
TTTTCACTGG GCTGGGAGGC TGATATTATC TAAATATGCT GAGGAGGTT CAGTATCTCC 109380
ACAACCTACC TCAGAGTGAA TGCTCCCCTC GGCCTTAAGG CAATATAAAC CAGCCCTGTT 109440
TAGCAGGATA GCAAATGTT TGCGGTTGTA AACTGGTGTG CCATTGGCTG TGGCGCTTGT 109500
GGTGTAAGA ATCCCTGTGC TTGGTAATTA ATAGAGAAAT TCTATATTTT AAACCTCAGT 109560
TGTATATTGG CTCTTATCCA TGGCAGATTT TCACGTATGT GTTATTTTTT TATTATTCA 109620
GAGCCGGAGT CTCGCTTTGT CGCCAGGCT GGAGTGCAGT GGCGCGATCT TGGCTCATTG 109680
CAGCCTCTGC CTCTGGGCT CAAGCAATTC TTCTGCCTCA GCCTCCCTAG TAGCTGGGAC 109740
TACAGGTGCA TGCCACCACG CCCGGCTAAT TTTTGTATT TTAGTAGAGA TGGGGTTTCA 109800
CCGTGTTGCT CAGGCTGGTC TTGAATTTCT GAGCTCAGGC AATCCGCCCCG CCTCGGCCTC 109860
CCAAAGTGCT GGGATTATAG GTGTGAGCCA TCATGCTCGG CCCTATGTGA TATTATTAC 109920
AATGAATTCC AATGATCAGA CCTATACTCA AGTATAAGTG AATATATCAT TCAATGAAGT 109980
ATAAATGATC ATTATGTTCA TATTCACACA TACAATAATG TACTCAAGTT TATTGCTAAG 110040
GTAATTCAGA ATCTCCTTAT TTTGAAGTGT GCATTTGATA TACCTGTTG GGAATAACTA 110100
GTTTCTTATC TTTGACAGAA AATAATTTT TGTGTTTGT TTTACTAAAA AAGCATGGTG 110160
AAAAATGGCT CCATTTCTAA GAGAGGTAAC TAAATATCG CAATTTGCTG GGTGTCATTA 110220
AAGTAACTCA CAAGGGAAAA AATGCAAATT GGTATCTGCT GATGGAGTAA ATCTCCGCAG 110280
AAGTGATGAC CCTGAAAGGA TCAATATATT AAAGCCCCTC CCAGCTGGTC ATTCCAGATT 110340
GCAACAATAA AGCATTAAGT GTTAAACCT CAAGGCAGCT TTTTTTTTTT TTTTTGTCT 110400
CAAGTCCTTT ATTATTAATT TTATAGACCT ACTTAATTAC TAAGCCAAAA AAAATCAAAC 110460
TTGTTTCTCT TTGTGACTTG TCAATAGTAT TAACTATTC TGGTTTTTA TTTTGTGTT 110520
ACCTTAAAGT CTCCAGTTTA GTAATTTTTC TGTACCTAAA CACTTCGGAT TTGACATGCT 110580
TTGTGGCCTT TATCAGTAGT TAGAATGTAA ATCCAATAA TAAAGTAAAA GCCAGGTCTT 110640
CAAAACCTGG GGGCCAAGAA CTCTGTTTGA GAGGGCCTGT GACTCTCTTG GACACTGGAC 110700

FIG. 6.42

AAAATCTCAT CTCTAAATAT GGATATTTTA GGGAGAGGGT CTTTAGGCTG TCATTTGGAT 110760
TTTCACAGGG CTCCATGTAT CCATAAGGTA GTCTCTTGGG AAGTTTGACT TCAATAAATG 110820
AAGTTTAACT TAAACCTAAA ATGAAATTTA ACTGAAAAAC AAAATCCAAT GAAAGATGCT 110880
TTCTTATGCA AAAACAAACA AACAAAAAAA AACAAAAAAA ACCCAAAAA ACCCAAAGCC 110940
AAAGATTGTT TCTGAAATTA GGTTCAGGT TCCAGAGCAA CTCCATGGTG GGAATCAGC 111000
CACATGTAAA GTAAGCTAAG AGTTTGGACA ATTTGTAATA TTTATTCCTA GGTTTCTTTA 111060
AGACCTTTTC AGATTTTGAA TTCCTATTAG TAGCATCAGC CAGGTTCTAA ATGTAGGCAT 111120
CACCATAGAC ACTTCCCCAC TGCTGCAGTC CCCAACACTT GCCCAATTTT CCCTTGAATT 111180
GCACCCATGC TGCCTTCTCC AGGCCTATTT GAACCCAGAA CCTCGTTGTG CCTCGTTTGA 111240
AATATAATTT CCTCCTAACT AGTCTCTGAT CTAATTTTTC CCTACATTG CTGCCACACT 111300
AATCACCTAA AATAGATTTT ATTCTACCCT GAAACAGAAA TCTCTAATAA GTTACTCCCT 111360
TCCCTTACGG GGTAAGTTA GCCACATCCT AGGTATTCAA GGACCTTCCA GGAGCTAAGA 111420
ACATTTCCCC TGCACCTTCT TGAAGTACAC TTGTCCTATG TACTGGTTAT GTTCATTTCT 111480
TACCCTCGCT CTCGTTTTGT CTGGAATTTT CTTGGCCTT AAATGCCTCT CACCTGCCTG 111540
CCCACATCTC TCAGGGTTGT TTCAAATCCT CAATGAAGGC TCACAGCCCC AGTCTATGTT 111600
GGCCACTTAC TTCGTGGCCT GGAACATTTT TTCTTTGGCT GACTTGCTGA CACTCCATCA 111660
GATGCATTTT TATCTGGTTG TCCATCTGTG AACCATACCC TGAGAAGGCA GAGAGTGCCT 111720
CTGCACTGAA CATGTGCTAG GGGACAGGTC TGTGCTAGAG GGGCAAGCAC TGGGAATGAA 111780
GAACTGGTCC CTAATCCCAA GGAGTTCATA TCTCAGTGGA GGTGACAAGC AACTCACTGT 111840
TTCCGGGGGT TGTGGTGACT GCTGGGAGAA GGGGTGTCTA TATTAGATCG AAGCAGCATC 111900
AGGGGAGGTT CCCTGAGAAG GTGATGCCTC AGCGGATGTC TCCCAGCTAA GTGGGGTGGA 111960
GGTGGAAGA GGCAGAGCAG GGAGAGGATC TAGGTGGGGC GTGTAAGTCT GCATGGGTAA 112020
CTCAGGGAAC CCTTGGAAC TGCATGTAAC TGTGTGAAGC TTTCATGAAG GAACATGGTA 112080
GGAGACTAGG GTATGGACTA TAGAAGCCCT TTTGCTAAGC TCAAGAATTT GAGGCCGGA 112140
GCGGTGGCTC ACGCTGAAA TCCCAGCACT TTGGGAGGCC AAGGCGGGCG GATCAGAGG 112200
TCAGGAGATC GAGACCATCC TGGCTAACAT GGTGAAACCC CGTCTCTACT AAAAAAAAAAG 112260
TACAAAAAAT TAGCGGGGCG TGGTGGCGGG CGCCCGTAGT CCCAGCTACT CAGGGAGCTG 112320
AGGCAGGAGA ATGGCATGAA CCCGGGAGGC GGAGCTTGCA GTGGGCGGAG ACTGTGCCAC 112380
TGCACTCCAG CCTGGGCAAC AGTGCAAGAC TCCATCTGAA AACACAACA ACAACAAAA 112440
ATTTGAAGTG TATCTTGAAG GAAATCCCTT GGAGCCTAAA AATGATCATT GATAACAGAA 112500
AATGATCTCT GCTCTGCCT AGGGTAATAT ATTCAGCTTC AAAGTGGAAG GGCATGTTTT 112560
CCAAGGGCAT GTTTTCTAAG TCCCTGTAAT TGTAAGTATA GCAATATAT GCCCTGCATC 112620
TTGAAATGTA AGACTAGGTT TGAACAGTAT ATAAATTATC TTATGATCTA ATTTCCCTC 112680
ATTTTGTGGT TTCTACTATA AGCTACCCAG AAGTGTAAGC AGGACGTTTG GAATTTGATG 112740
GGCATCGGAA AGATTCTAC CTAAGAACAT TTTTTTTTTT TTTTTTTTTT CTGAGAAGGA 112800
GCCTTGCTCT GTCACCCAGG CTGGAGTGCA GTGGCACGAT CTCAGCTTAC TGCAACCTCC 112860
ACCTCTCAGG TTCAAGTGAT TCTCCTGCCT CAGCCTCCTG AGTAGCTGGG ACTACAGGTG 112920
TGCACCATCA TGCCTAGTTA ATTTTATAT TTTTAATAAA GGCAGGATTT CACTATGTTA 112980
GCCAGGCTGG TCTTGAATC CTGACCCCAT GATCTGCCCA CCTTGGCCTC CCAAAGTGCT 113040
GGGATTACAG GTGTGAGCCA CTGCGCCCGG CCTCTAAGAA AATTTTGTAG AGCTACTTGT 113100
TCTGTTGCCT GGAATTCCAC CGTAAGTACG ACGTTGTGTC TCCTTCTCCA GGGCTACTAA 113160
CTAAACAACA GAGGGTATTG TGTTATCGAC AATTATTTGA TTGATAACTA TCAGCAAACA 113220
TTTGCCAAGG CATTCTTTA AAGATAGCCT AGTGACTCTA TTAATACTC CTTCTTCCAG 113280
GCTTCTAAGT TCTGTTGGAG GTAAGTAGAT CCCAGAGATA AAGCACCTAC CATAGGACCT 113340

FIG. 6.43

GAATCTTGGT AGAAATAAAT TATATCATCA TGTTATCATA TTATCATGTG TTTTCTATC 113400
TTTAAAGTCT TATGTGAATA TTCTGCTTGA AAAATATGTG TCCTCTGTGA GACCAGAGTT 113460
GAAAATATGT TATTCAAGAA CTTGTAACAG GAACCCGCAC AATTTCTGCT GGAGTTTAAT 113520
TTCAGGGTTA ATTCTGTCAG CAATCTAAGG TAAACATTAA CATTTTCCC TAGATTCAAG 113580
TCCGTTGTCC AAAAGCTGTA ACAGAACTTA ACTGAATAAA TAGTTTCTTA AGATGGTAAG 113640
CTTCCATATG CTTATAATGA CTCCTCTACA CGTTTTCATC TGGAAGGCTG CTCATGCTTT 113700
TGGAAGCAAA GAAGACAATC TTAATAACT ACATTTGCTT TTTGGTGGTG CCAGATTTT 113760
CTGAGAAACA CCAATGGAAT TTATAAATC ACCAGTCAAT GGGCAATTGA GTTGCTGTTT 113820
TGCTATTACC ACTGCCGTTT GTGAGCATTG TTGGGAAGGT GTCTTGAAGC ACACGTGCAA 113880
GTTTCCCTTG GATAAGTAGT AGGAATAGAA TTGCCAAACC ATGGCTTCCA GTGCAGACAC 113940
AGTCTCTCCC TTGGGCCAG CCACTAGGCA CCACACATTA AGAGGATATT GTCTGTCCAT 114000
GTCCTAGAAA CGTTGTAGCA TCATGCTCCT ATTCGATTAA AAATCTCATT ATTAATGA 114060
ACCATCGGGT AAATGTTGTC TCGGGAAAAG AAGCACTGAC CGTCCCTGGG TGGGCTCGAA 114120
CCACCAACCT TTCGGTTAAC AGCCGAACGC GCTAACCGAT TCGCCACAG AGACCCAGTT 114180
ACTCAGGCCG CGCTGCGGTG TGTACAGATT TCCGCGGCGC CGGCAGCCGC TCTAGCCACC 114240
CTGGGCGTCG CCACCCAGG CGTTGCCACC CCAGGCACGG GCTGAGAAGT CGCGGGGCGC 114300
GCCGAGGAGG CAGCGGAAGC GGCCGAGGTG CCCAGCGGCC GCCGCGGGG GAGAGGCTGT 114360
GCCCCGCGC GCGGGAGGGG GCGGGCGAGG CCGCGTGA CTGGGCTTCT CTGGGGACGA 114420
AGCGCGCCCC TCGTGCGGC AGCGGCCAGT GGTCCGCACT CGGCCCGAC TCGGGTAGG 114480
AAAGATCCTC TCAGCAATGG CTGCGCGCCA TCGTGCTCT GCGGCGGGGA CCGTGCCGGC 114540
CGGGCGCGCC ACCAGTAACC AGGGACCCAG GGGAGAACC GCAAGGGGA ATAGGTCGA 114600
CGGAGAGAAT ACGACACGCT TGGAGGGAAG AACCACGTGC TGTACAGTT TAAAGGATGG 114660
AGAGTCACGT GCGCTTAGGT CCCAACTTA AGGGACCTAA CCCTTTTCT GGGTTGCCG 114720
TATTGCCCT TCTCCTAGA CAGTTTTTCA TCTCATCACC TCTACCCCG TAAATGCAA 114780
CGAACATAGA TAGGCTGTGT ATCAATGTAG ACTGTATGTA TATCTGTGCT TCGTACATAA 114840
AAAGAATATG ATTTTGGCA CCTTCTAAGA ACCAATTTGC ACCCCATTTT GAGGCATATG 114900
GCCTCTGTTG AGATTGCATA GTTTAGGGGA CATCAAAAA GCCTTATAGA GGGACTGGCA 114960
ATTAAGATAG CCTTTCAGTT TGAAATGGCC ATTGAAGGCT TCTCCCTTC CCTGACTTCT 115020
GAATTTTTT TTTTTTTTT TTTTTTTTT TTTGAGATGG AGTCTTGCCC TGTTGCTGGA 115080
GTGCAATGGC GCGATCTCGG CTCACTGCAA CCTCCGCTC CCGGGTTCAA GCGATTCTCTG 115140
CCTCAGCCTC CCGAGTAGCT GGAATACAG GCGCCTGCCA CCACGCCAG CTAACCTTTG 115200
TATTTTAGT AGAGGCGGGG TTTCGCCATG CTGGCCAGGC TGGTCTGGTA CTCCTGACCT 115260
CGTGATCCGC CCGCCTCCGC CTCCCAAAGT GCTGGGATGA CATTACAGGC GTGAGCCACC 115320
GTGCCCCGCC AATTTTTTTA GGCGCACTGT TCAGTGGCAC TAAGTACATT CACATTGTTA 115380
TGCAACTATC ACCGCCATCC ATTTCCAGAA CCTTTTCATC TTCCGAAACA GAAGCTCCCT 115440
ACCCATTACA CGGTAACCTA CGATTCCCTT CCTCTAGTCG GAACAATCAC CATTCTACTT 115500
TCTGTCCCTT TGAATTTGAC TACTCTAGA GACCTCATGT AAATGGAGTC ATACGGTGTT 115560
TGCTGTGGC TGGCTATTT CACTTACCAT ATGTCTTCAA GGTCCATCCA CGTTGTAGCC 115620
TGTGTCAGGA TTTCTTCCT GGATAAGGCT GAATAAGCTG CACTGTATGC AGGTATCGCA 115680
TTTTGCTTTT CCATTCATCT CTCCGTGAAC ATTAGGGTTG CTTCCACCTG CAGCTATGAA 115740
CATGGGTCTA CAAATAACTG ATTCCTGCT TTCAATCTT TTGGGAATAT ACCCAGAGAT 115800
GGAGTAGCTG GATCACATGG TTTGCTATTG GCTGTACCAT TTTACATTCG CACCAACAGT 115860
GTACAAGAGT CCCTATTTCT CCTCATCTAT TTTTTTTT AATAATGGGC ATCTAATGG 115920
GTATGAAGTA TCATCTCATT GTGGTTTTGC TCTGCATTTC TCTAACGATT AGTGGTGTG 115980

FIG. 6.44

GGCATCTTTT CCAGACACCA CCAATCTGAA TTCTATGGCC CTTGTTTAC TCACTTCCTC 116040
CCAGCAAGAG CCATTTCTGC TTCAGCAAGG AGGAAGCTGC GACTGATAGA GGGAAAGGGC 116100
CCAGGGGGCT TGCAGAGTGG GGCCTGTGCC ATGCAAGGAG AGGAGAAGAA GGTGGATCTT 116160
TGAGTAGGAC TATCTGGAGA TCCTGCTTTC ACAAGGTCCT TGCTTGTGTG CTGGGCAGCT 116220
TTTGAGCTA GTTATCTTTA TTTAGCCCT TGAGGGATAT TTAGGCATGT GGTGCTTGTG 116280
AGCAGCCAAT CCATGAAGAA GGAAGTATG GTCTCCACCT TGGAAATATT GGAAGAGATA 116340
ATGCCGTCCA AATTGCAGTT TTAGAAGTTA ACTTAAAATT ATGCTATTTT AATGGAATTT 116400
TGGGTGCATT TCCATTTTCT TCTTAAGAAT TGCTGGAATT TCTTAAGTGT TTAGGTGATG 116460
ATCTCTTTT GTGATTCCTT TTTTAAAAA CAACAACAAA ATCTTTCAAA TACATAAGAA 116520
ATAGGCCGGG CACGGTGGCG TAATCCCACC ACTTTGGGAG GCCGAGGAGG GCGGATCATG 116580
AGGTCAGGAG ATCAAGACCA TCCCGGCTAA CACGGTGAAA CCCCCTCTCT ACTAAAAAT 116640
ACAAAAAATT AGCCGGGCGT GGTGGCGGGC GCCTGTAGTC CCAGCTACTC GGGAGGCTGA 116700
GGCAGGAGAA TGGCATGAAC CCGGGAGGCG AAGCTTGCAG TGAGCCTAGA TCGCACCCT 116760
GTACTTTAGC CTGGGCGATG GAGCAAGACT GTCTCAAAAA AAAAAAAAAG AAAAAAAAAG 116820
AAAGAAATAG ACCTTTATTT TTCTGTAAT CCACAAAATT TCTATTTTGA TTCCCTATTA 116880
TTTTGCTATT GTCAACACAG TCTCAGTCAA TTCAAGATCC TGTTTGTGCC TTTCCCTGGA 116940
GTCATTTCCA AGTGCTAAGG CTTTGGTCCA TGAGTCGCAT GTGCACACTC ATGGCTGTAG 117000
AGGGAGTTTT GCTCCCGGTG AAGGTCTTGG TGGCTCTTCT ATACCTTGAT TGAGGGAAAG 117060
GAATCTTATG TGAAGTTAGC TTTGTTGTAT CAGATATTCC ATAAAGCCAT TTCTGGGACA 117120
GTCCCTCTG TTTATCGGAC CACAAGCTTC TCTGTCTCA TCAAGCCAC CTTTATACTT 117180
CATTTCTCCA GACTTCATGT CCAGACTGTG GGATGAACAA GTGGTTATAA GGTTTTAGAG 117240
GCTCCTGTAG GACTAGATGG AAGGCAAAAA AAGGAAATAA CCTTTAAGCA TGCTCTCGAT 117300
TCCTTAAATC CCATCTGAAA GTCTTAAGGA TGTCTTCTCA GTCATACTTA TTTGACAATA 117360
TTACCTAATT TTCTCCATTA GCCCAAGCTC AGGGGTCTTT CTTCTTCCAT ATTCACATGG 117420
GTGCAATGGT TTTCTGAAAG GAAAACAGCA TTACTAGGGC AGTAACATTT AATTAATCAC 117480
AGGTACTTAT CAAACTACAA AACAGGCATT CCAGGAACTG GGTGTTTCTG TTTGTAAAAT 117540
TACACTCTCG TGTACATGCT CCCACTAAAA TGTAAGTTCC CTGAGGATGG AGGTTTTGGT 117600
CTCTTTGCTC TGTGCTGTAA CCCCACACT GCAGCAGGGC CTGGCACATA GCAGGCATGC 117660
AGGGACTATG CACTGAATCA ATGAGGAAAT GAAACCAGG ACCATGAAGT AAATCTGGACA 117720
AAATAAAATG TGATAGAAAA TCTAAATTCC TAATACATAA GGAGCACTTA TCAATTGATA 117780
TTTACAAAAT CTTTTTACAA TTCAATTAAA GACAACATAA AACAAATAAG AATGGGGACA 117840
GGAACAGAAA ATTCCCCCAA AGAAAAAAT ATATATACAT GGTACAGCCA TTGTGGAAAG 117900
CAGTATGGAG TTCTCAAAAA TATTAAAATA GAACTATCAT ATAATCCAGC AATCCCATCC 117960
CTGGGTATAT ATCTAAAGGA AATGAAATCA GTACCCCAAA GAGGTGTCTG CACTCCCATG 118020
TTTATTGCAG CATTAGTTAC AACAGCCAAG ATATGGAATC AACCCATCAG CAGATGAAAG 118080
GATAAAGGAC ATGTGATACA TATACACAAT GGAGTAGTAT TCAGCCTTAA AAAAGAAGAA 118140
AATCCTGTCA TTGCAACAA CATGGATGAG CCTAGAGAAC ATACTAAATG AAATAAGCCA 118200
GGCATAGAAA GACAAATGCT GCATAGTCTC ACTTAGGTGT GGAATCTAAA AAAGTCAAAT 118260
TAAAAAATA TGTCAGCAG AGAATAGAAT GGTAGTTGCC AGGGACTCTG GGAAGTAGCA 118320
GGGGTGGGGG TGGAGGGGAG GGGATGGGCA GAAGTTGGTC AAAAGGTACA AAGTTTCAGG 118380
TAGACAGGTG TAAGTTCTGG GGATCTATTG TACAGCGTGG TGAAGTAGT TAATACTGTA 118440
TTGTGTACTT AAAAATTGCT CACCAAAAAT GTTCTACCA AAAAAATGAT GTTTGGATAT 118500
GTAAACAGT TTGATTTAAT CATTTTGACG TGTGTGTGTG TGTGTGTGTG TGTGTGTGTG 118560
TGTATACATC AAAACATCAC ATTATATACC ATATACAATT AATATATACA ATTTTGTCA 118620

FIG. 6.45

AAGAAAAAAT GCACATGACC AATATGATAA AAGTTTAGTC TCACTAGTAA TAAAAATCAA 118680
AATTAATGA AATAAAATT TCTTTCCCCA AATCGCAAAA GAGAAAGAAA GGTAATACTA 118740
AAACACAGTC ACGGTGTAGT GAGAGGGCTG CTCTCACACA GGA CTGATGA GAATAAAATT 118800
GGAGAGCAGT GTGGTAATAT ACATATTAAC CAATGTATAT ACCCTCTCAT TTTAGAAATT 118860
CTATATTAGA AATCCATCCT AAGAAAATAA CCAGGGATGT GATCAAAATT TTGAATGCAG 118920
CAGCACAGTA TTATTTATAA TAGTTATAAA TAAGAAACAA CCTGAATGTC CAGCAACAGG 118980
CAAAAATGAT AAATAAATTG TGGCATATTT AAGCTGGTGG CTCATGCCTG TAATCCCAGC 119040
ACTTTGGGAG GCTGAGGCAG GAGGATCTCT TGAGGCCAGG AGTTTGAAAC CTGTCTGGGC 119100
AACATAACGA GACCCAGTCT CTACAACATA TTTTAAAAA TTAGGTGGGG CATGGTAACT 119160
CATGCCTGTA ATCCCAGCAC TTTGGGAGGC TGAGGTGAGC AGATCACCTG AGGTGAGGAG 119220
TTTGAACTA GCCTGGCCAA CATGGTGTA CACCATCTCT AAAAAAATA CAAAAATTAG 119280
CCAGGGTGGG GTGCGTTCCT GTAGTCCCAG CTA CTGCGCA GACTGAGGTA GGAGAATCAC 119340
TTGAACCCGG GATTGCGAGG TTGCATTGAG CTGATATCAT GCCACTGCAC TCCAGCCTGG 119400
GTGAGACCT GTCTCAAAAA AAAAAAAAAA AGAAAAAGAA AAAATTAGCT GGGCGTGGTG 119460
CTGTACGCCT GTAGTCCCAG CTATCCGGA AGCTGAAGCG GGGGGATTGC TTGAGCCAG 119520
GAATTTAAGG CTGCAGTGAG CTATGATTGT GCCACTCCGC TCCAGCCTGA GTGAGAAAGC 119580
AAGACTCTGT CTCTAAAAA AAAAAAAGTG ATATATTTT AAAATAGAGT ATATTACTTA 119640
TATAGACATC AAAACAATA TTTTCAAGG ATATTTAAAA ACATAGGATC ATGACAAAAT 119700
GTAAAGTTCA AAGGTAAGAT GGAGAATGGA GAACTGTGGG GAACTGTATA ATCTGACAAT 119760
TCGTAGTTGC ATACATCTTT CTGTGTGCTG GTGCTGTTAG AACACTTTGT ACGCATCACC 119820
TCATTTAAGT TCAGCATCCC TAGGTGGCAG ATACTATTAT TATATTCCAG TTTTGTTC 119880
CGTTGTATAT GCGGTGTGAG CCCCAATATG GGATGTGTGT GTGCACATGT GCAGTATTTG 119940
GAAAGTTCTA TGAAATATTA TTAGTGTTA TCTCTGGGAG GTGATTTTTC TTCCTTTTCC 120000
AGTATGTTCT CAAGCATTG CTGCAAGCAG TCTTTTGGG GGCAGGGT GAGAGGCAGC 120060
AGCAGTTTCC CTAAATTACA GATAGAGGGA GGTAGGTGGT TATGCTTGGC CAGATCTCTG 120120
TCTAGGGGTA GAGGAGTGCC TGTGTGTGGG TAGGGACACC GGCGGGGGGC TTTGCCAAAC 120180
ACAGTGGAAC TGTCACGCTG GTCTCTCTT TCACTCTTT CACTCACCTG AGAAAAGGGT 120240
GTCTATGGAC CATGCACACT TCTGTGGGGA ATTTTACAAG ATGTGAATCA TCAGTGATGA 120300
AGATGCTTTC ATTTAAAAAG AATTGGAGTA CCTGAGATTA GAGATAACTT CTACCTTTT 120360
AAAATATTTT TAAAAATTC TTTGCACTGA TTTTCTTCT TCGTTTTTAT GAGTTGTTTT 120420
CATTTGGGTG GGATAACTCA ATCTACAGGA GAATATTAAG ACTTTTAAA TTTTAAAAA 120480
TATACTTTCA AATACTTAAT ACATTTGTG TTAATGACA GCCAGCAGAT ATTGACTGAA 120540
TTGGGCTAGA TGCTTCAGGG ATCTCCCTTC CATTTAAGAC TCTCCGAGAG GCCATTCTG 120600
ACTGCAGGTC ACTGTATTAT TTTTAATTT AAAATTTTTC CTTACTTATT TTATTTAATT 120660
TTATTTTTTG AGACAGAGTC TCACTCTGTC GCCAGGTTG GAGTGCAGTG GCACAATCTC 120720
AGCTCACTGC AACCTCCACC TCCCGGGCTC AAGCGATTCT CCTGCCTCAG CCTCCTGACT 120780
AGCTGGGGT ACAGGTGCAG GCCACCACAC CCCGTTAATT TTTGTATATT TAGTGGAGTC 120840
AGGGATTGCG CATGTTGGCC AGGCTAGTCT CAACTCCTG ACCTCAAGCG ATCCTTCCAC 120900
CTCAGCCTCC CAAAATGCTG GGATTACAGG CCTGAGCCAC CCCACTCGGC CTACTTTATT 120960
AATCCACTTG CAGAAACAGG ATATACACAA AAACGTTTCA AGGCTGTAAG TGCCACTGCA 121020
TGGCACCAAT GGTAACGTT TTACAAATTT GAGTCAGGAA CAATCATTAG TGCTACTAGC 121080
AACAAAAATC AAAATTAAT GAAATAAAAA ATTTCTTTCC CCAAATGGCA AAGGAGAAAG 121140
AAAGGTAATA CTAACACGCA GTCAGGGTGT AGTGAGAGGG CCGCTCTCAC ACAGGACTGG 121200
TAAGTACAGA GCCATGGAGT AAGCAGGTCT TGAGCTGACA CTGGAGAGGA TCCTTTTTTT 121260

FIG. 6.46

TTTTTATTTT TATTTTTTTA GAGTCAGGGT CTGCTTTTT TACCCAGGCT GGAGTACAGT 121320
GGTGCCATCA TAGCTCACTG CAGCTTCAAA CTCCTGGGCT CAAGAGATCC TCCTGCCTCA 121380
GCATCCCCAG TAGCAGGGAC CACAAGTGAG AGGATCCTTT AGTGTGTGCA AGGAGAAGGA 121440
ACAGAGGTGT GGATGGGTGG GCACAGACAC AGGAGCACAG CTGAAGCAGA GGATTACAAA 121500
GGGTGGAGCC TGATGTAAAG AAACCTAATA GGTGACAGAG CATGGAGGCT CTTGAATACC 121560
AGGCTGGAAA CTGCATTAGG AACGGTGCTC ATAATTGCAG AAAATTTTAC ATGGCCTAGA 121620
TAGTCATCAA AGGATGATGT ACAAACAAC ATGGCATATT TATACAATGT GCCGACAGGA 121680
TGCACTGAAC ATTTTGAACA ACAAAGAGAC TTGATAATGG CGAGGTTTTG AGGAGGTGAA 121740
TCAGGATGCA AAAAAAGCAA ACAACTAATA AAGTTGATTG ATGACAAACA CTATCAAAAAG 121800
GCAGCCAGGA GAAAAGCTAC TGGTTACCTC CAGGGAGCTG GTGAGGGAGG CTGGGTGGGA 121860
GGATCTACCC TTCTGAATTC TGAGGGCACC TCCAGTGTGG CCCTCAGAAA GCAGGAGCTT 121920
CCAGGCTAGA ATCAGATCCC GACATCCCTG TTAATTCCAC GGATTCCACA CCGAGTCAGA 121980
TTTATGATTT ACTATAGGGT TTTAAAAACC AAATTGCAGG GATGCTAGCC TATCAGAGCT 122040
TATCTCAGAC ATTGTCCACT AAGGTATACA GAGTGCTGCC TGTTCTTTG GTACCCTAAT 122100
CAGGAAACCC CATCAGATCT GCTCCTTCT ATGGGGTAGT GAGTAACACG AAGGCTTACC 122160
ATCTCACACA GATAACTGGT CATAGGTCCA GCAGAAGTTT AAAACAGAAA ATGAGGAAAG 122220
CCATGTGATT AACTGCTGCC AGACTGTTTG TGTTACAAAC AGCAGTTCCT TAGGCATTGC 122280
CTGGGACATG CAATAATTC TGTTACACAA TCTGTGGTAG TTAATGCT GCACGATGAA 122340
AGCTATCTGA TTTGGATTCA TTATTAGGTG AGCCATCTCG TCTGCAATTT GTTCCACCA 122400
TTTTCATTTA ACAAATGTAA AAAAGTTTAT TAAGCTCTTA CAAAGTTATG CTGGGCAAAT 122460
ATGCAAAAGT CCAGATCACC TACCGCAGGA ACTAATCTAG CCTCCTCTCT GGGCACCCCTG 122520
TTGTTTGGGG CTGGGCAGTT CTTTCTGTG TAGAACCATC TAGGGCTGAA TAGGTCATTC 122580
TGACACCTGG GCACCTCTGC CTGCTCGTAA ATGGGACAAT CAGAAAGGGC CTTATGTTT 122640
CCAACTTTC TTTAAAGTAG CTGTTCTGAA AACATGGTCC AGGGACCCCT GATTGTCCCT 122700
GAGACCTTTG AGGGGATCTT CAAGGTAAAT ATTAATGTCA TAATAATACT AATATGTTAT 122760
CTGTCTTTTT TCACTCTCAC TTTCTCACAC GTGAACAGTG GCATTTTCCA GGTGACAGAG 122820
TGTGTGATAA TGAACCTAAC TGAATGCAGA AGCAACATG AGAACCTAGT TTTTCAATC 122880
AAACCAGACG TGAAAGAGAT TTGCAAAAT GAAAAACAA TGCTATCCTC CTCACAATAT 122940
TTTTGTTTTA GAAAATAAAG TTATTTTCC TAGAAATGTT TTTGAGTTTA TCAGTCATAG 123000
GTTTATTATT ATAATTAATA AATGAAATAT ACATACACAG ACATATTTT TAAAGTTCTC 123060
AGTTTAAATC TCTTTTTTTT TTTTTTTTTT TTTGAGACGG AGTCTCGCTC TGTCGCCCAG 123120
GTTGGAGTGC AGTGGTGCGA TCTCAGCTCA CTGCAAGCTC CGCCTCCCTG GTTCGCGCCA 123180
TTCTCCTGCC TCAGCCTCCC GAGTAGCTGG GACTACAGGC ACCCGCCACC GCGCCCGGCT 123240
AATTTTTTGT ATTTTAGTA GAGACGGTGT TTCACCATGT TAGCCAGGAT GGTCTCGATC 123300
TCCTGACCTC GTGATCTGCC CACCTCGGCC TCCCAAAGTG CTGGGATTAC AGGCGTGAAC 123360
CACCACGCCC GGTCTCAGTT TTAATTTCTA ATACAGTAAG TATTGATCAG TGTGCCCCAC 123420
ATTAGTAAAA GCTCTTGGGG TCCTCAGTAC TTCTTTTAA GAGTTGTCAA GGAGTCCTGT 123480
GACCAAAAAT AGGAGAGCCA CTGCCCTAGA AGGACAGCCC CAGCCGGGT CAGGAACAAC 123540
TGGGACAGAA CCTACTGCTC CTAGTGGATT GTAATATGAT AGGATTAAAC CTTCAAGGTT 123600
TCAACTCTTG GCAAGAGTCC ATGAGGGGCC ATGGTTTGTG CTGAGCATTG CTTACTGTTA 123660
ACAGGAGCAA GTTCCTTAGG CTGGTGAGCC AAGCCAGCCT GACGCTGGCC ATGGACATCT 123720
TAGTGGGCTG CTTGTTCTAG TGTGGGTTTT CATTTTATGG GAAATGTCAT CTGCTCTAAG 123780
GCTCTTCTCA TTTGGGGAAA TCACAAGTTC TCAGAATGTT TGTCTCTCTT GTTGGGGGCC 123840
TCTATAATTA AATTATAAAA CAGAGGTAAT GGTTAAGTAA TGCAAGATTG GACAGAAACC 123900

FIG. 6.47

ACAGAGGATT TAGGGTTTAA TTTGAGTGAG GCAAAGGGGG GATGAAGATG AGCGGTCCTG 123960
GAGACAAGAA AAAGATTGGA TGAAGCTGGG CACGGTGGCT CACGCCTGTA ATCCCAGTAC 124020
TTTGGGAGGC CAAGGTGGGC AGATCACTTG AGGCCAGGAG TTTGAGACCA GCCTGGCTAA 124080
CATAATGCAA CCCCGTCTCT ACTAAAAATA CAAAAATTAG CCAGGCGTGT TGGTGTGTGC 124140
CTGTAGTCAC AGCTACTTGG GAGGCTGAGG CATGAGAATC GCTTGAATCC GGGAGGCAGA 124200
GGTTGCAGTG AGCAGAGATC ATGCCACTGC ACTCCAGCCT AGGCAACAGG GTGAGACTCT 124260
GTCTTCTTTT TTTTGTAGAC GGAGTCTGTC GCCCAGGCTG GAGTGCAGTG GCATGATCTC 124320
TGCTCACTGC AAGCTCCGCC TCCCAGCTTC AAGCGAGTCT CCTGCCTCAG CCTCCCGAGT 124380
AGCTGGGATT ACAGGCATGT GCCACCACAC CCAGCTAATT TTTATATTTT TAGTAGAGAC 124440
GGGGTTTCAC CATGTTGGTC AGGCTGGTCT CAAACTCCTG ACCTCGTGAT CTGCCCCGCCG 124500
CGGCCTCCCA AAGTGCTGGG ATTACAGGTG TGAGCCACCA TACCTGGCTG AGACTCTGTC 124560
TTTAAAAAAA AAAGAGAGAG AGGGAGAGAA AGATTGGATG AAACAACAGA GTGGGGAGGA 124620
CCTGTGAGCT TGGTAGCTTG GTGAAGGCAG GGCTTTATTG GGGGCCTTAG AGGGGATCCA 124680
ATAAAGGTTT CCAGTCATGG TAGTGACCTA AAGAAAATAG CATTTTAACA TCTTTCATTT 124740
CATAATAGAC AGTCACAGTT TACAAGACCC TTTCCATACA TTCCTTATGA CATCCATACT 124800
ACAGCCCAGA GGCAAGTTGT GCACTCTCTC CTCTCACAAA TACAAAACT CAGCCTCTAG 124860
AGGCCAGCGA CCTGCTCAGG GTGATGTGCA ATTCAGGGAT GACAGAGTCG AGGCTCCCAG 124920
CCCAGTGTTT ATCCCTCACA GGCACGTTGC CTGTCACTGT GCAGTATAAA ACTTTGTACA 124980
AGAAATCAAG TTGCATTAGT CAGTCGGATT CCCCAATGA TCACATTGTA GATGGTGTAT 125040
GCTGTGGGCA GAGCAAGGGC TGCTGTTTCT TGGGCAAAAC AATCAGTCCC CCTCCCCCCC 125100
AAAATAATG AATGCCAATG GTGTGACTT ATTTATTTA TTTTATTTT ATTATTATT 125160
GTGAGACAGA GTCTCACTCT TTCACCCAGG CTGGAGTGCA ATGGCATGGT CTCGGCTCAC 125220
TGCAACCTCT GCCTCCTGGG TTCAAGCGAT TCTCCCGCCT CACCCTCCCG AGTAGCTGGG 125280
ACTACAAGTG CATGCCACTG CACCCGGCTA ATTTTGTAT TTTTTTAAAG TAGAGACAGG 125340
GTTTCACTAT GTTGGTCAGG CTGGTCTTGA ACTCCTGACC TCATGATCCA CCTGCCTCAG 125400
CCTCCCAAAG TGCTGGGATT ACAGGCATGA GCCACCGCGC CCAGCAATGT GACTTTATAA 125460
TTACAGAATG TAGGACTCAG CTCCCACTAT TGTTATGACT CAATATTCTC TTAGATAATG 125520
TTTGGGGCAC TAGCTTACAG GCAGCATTGC CCGGTGGTTA ATGTTGTAGC TTTGCAGGCA 125580
GACTGACCAT ATTAATAATC GATCACACCA TTTGCTAAGC CTGTGGACTC GGGCAGCCTT 125640
CTTTCTCTGC GTTAGTTTCC TCCTCTGTAA AACACGGATG ATGCTATAAA CACACCCAAG 125700
TCCTAGAATT GTTATATGAG TTAGAAAAGA TAGGCAAATA CAACTCTCAC AAGACAGCCT 125760
GGCCTCCAGT AAGTGCCACT GAGTGTTTGC TCTTATTGTA CAGTGGCTCC AAGTGCTTCT 125820
GTCTTGATT ATTTCTGACC AGGTGGCTAT GTCTCCTAGT AACTTACCAA TCCTGTTGAG 125880
TCTTAATAAG CACGTCTTTG ATGCCTACAG TGCGACTGAA TTTCCAGGCC TCATTACTGG 125940
AGACACAATC ATCCTATATG CTTTTTCCA TTTGTTTTTA ATAAAGTGGT ACATGTGTAT 126000
GGCACCAGAT CAAACAGTAC AGAACAAGTT ACAATGGAAG AGAATGGCCT CCCAGCTTTC 126060
CTGAAATCCT CAACTCAGAG ACAACTTTTT TTTTCTGAC GGTTTCTTTA TACAGCCCTT 126120
TTTGTGGTTA CCTTCCTAAC TCTAGAAAAA CTATTCTTAC CTCTGTTTAT TTAATTAGAA 126180
ACATTAGACG TTACCTTTCA ACTCCTCAGT ATGAAGCTTT AGTTTTCAGC ACCCCAGGCC 126240
ACCACCCTCT TTCCAGGACT TACTACTTAT ACTGGTGGTA GGTGGAATTT TAAATTCAT 126300
CAGCATTCTT TTGTGATTCT CTGTGTGTTT CAGTTTTACA GCAACCCGTA CTTGTTGCAT 126360
GAGTACAGTA GAACTGGGAG GCTCATAACT TAGCCTGCAG GACTTTTCAC TTAAAGCCTG 126420
GCCCTCAGGG TGATGTCACC CACCTCATTG TGCCTGGCTC AGGAGTTTAG TCCCTCAGTT 126480
GCCTGGTTGT ATAGTTTGA TGTTACAGCAC CTCCAAATCT CACATTGAAA TGTGATCTCC 126540

FIG. 6.48

AATGTTGGAT GTGGGGCCTG GTGGGAGGTG TCTGGGTCAT CAGGTGGGTC CCTCTTGAAT 126600
GGCTTGGTGC CTTCCCCATC GTAACGAGTG AGTTCCTTGCT CTGGCAGTTC ACACAAGAGC 126660
TGGCTTTTTA AAGGAGCCTG GCACCTTCCG CTCTTCTCT TGCTCTTCTT CCTCCCTTCC 126720
TTTGTCATA AAAGCTTCCT GAGCCCTCAC CAGAAGCGGT GCAGATGCTG GTGCCATGCT 126780
TGGACCTCCT GTAGAACTGT GAGCCAAATA AACTCTTTCC TATAAATTAC CCAGTTTCAG 126840
GTATTCCTTT ATACAATGCA AAACAGACTC ACACATCTGG TAAACCCAG TTGTTTGCTT 126900
CTAGGTAAGA CGGGAGGAGT GGGGAGCTGG TGAGGGTTTC CACTGCATTG TCTATTTTCA 126960
GGCAAGGTGT CTCCACTGAG TAGGCTTCAC ATTCAGAGCT CTGGGTAAGG TGGGCAGGAA 127020
GAGGGTTGCA GGCTGCCCAA AGGAGGGAGA GAAGAAGGCT GAATCCTTCA GTGACAACCT 127080
GTGAACCAGA GTCTTAGCTC TCTTTGAATA TTTTGTTTCA TATCTTTGGG TTTTGTTTCA 127140
TTTTGCCTAG GGGTAAATGC TGACTGCCTG TTCTCTGGAC AGGAATGGAG AAGATGGTGC 127200
TAGCAGGGTT GCTGTTTATA TGATGACATT CATGCAGTCA CTCTCTTTTC AGCACACTTC 127260
TACTTCTGC CCTGGGTTCA GTTGCTGACT CTGAGCCCAG AAACCTTCTA GGGTTCTGTT 127320
AGGTAGATTG GCTTCCACCG TCTTTCGAC AACCACAGAA AATTCTAGAC TGTTTTCTCT 127380
TCGGGCTTCA TTAGTCAACT TGCTTCAGTC TGTCTTGCAT CTTCTAAATA TTTATAGATC 127440
TCTCTTTTT GTTGGAGTGG CAGAAAATGC TAGTTGACCA CCCAATATTC AAATTATCCT 127500
GCCTCCTTAA TAACAGAATA TCATTGGATG TGGTGGGTAA ATAATATACC CTAACCTTCC 127560
TTGCAGAGAG GGGTGGCCAA TGAGATGGAA ATGAAAGTCA TTGGGAAAGA CTCCCAAGAC 127620
ATCTCTTTAA ACAAGACAGA CTGAAGCAAG TTGACTAATG AAGCCCAAAG CTAGCAGTTG 127680
TTTTTGTTA TCTTTCCTC TTTCTTCTC TTCCTGTGGG GACAAAGGC AGTGATATCT 127740
GGAGCTGCAG CAGCCATTTT GGCATAATGT TGGAAAAGCC AAGAGACTCT CAGAGACCGC 127800
AGCTCCAGCA GTTTTTTATT TTTTCCAAAT ATTTGCTCCA CTGCAGGAGG ATGAGATATT 127860
CGTGTGTTG GCCTTGTGAC TGTAGGAGGA CTGCACTTCC CTGCCTTGT GTCAAGTTTC 127920
CCCATGTGGT CTGCTTTGGC CAGTAAACA TGAGTGGGAG AAGCTTGGTG AACCATTGCA 127980
TGTCTACCAG CTTTTTTGCT CTCTTCCCTT TGGCATTAGA AAGGCATGTC CAGGATGGAG 128040
TTGTTCTTC AGCCTAGATT GGGTTATGAG AAGCTAGCTG GGGGAGTCCA GTAACATATA 128100
AAGCGAGTTA GAAATAAAAC TTTGTTGTTG TAAGCTATAT ATATATATAT ATATATATAT 128160
ATATATATAT ATATATATAT AATATGTATG TAATATATAA ATACATATTA TACTTTAAGT 128220
TCTAGGGTAC ATTTGCACAA TGTGCAGGTT TATTACATAG GTATACATGT GCCATGTTGG 128280
TTTGCTGCAC CCATCAACTG CTCATTTACA TTAGGTATTT CTCCTAATGC TATCCCTCCC 128340
CAGCCCCCA CCCCTCAACA AGCCCTAGTG TGTGATGTTT CCCTTCTGT GTCCAAGTGT 128400
TCTCATTGTT CAATTCCAC CTATGAGTGA GAACATGTGG TGTTTGGTTT TCTGTCTTGG 128460
TGATAGTTTG CTGAGAATAA TGGTTTCCAG CTTCAATCGT GTCCCTGCAA AGGACATGAA 128520
CTCATCCTTT TTTATGGCTG CATGGTATTC CATGGTGTAT ATGTGCCACA TTTTCTTAAT 128580
CTAGTCTATC ATTGATGGAC ATTTGGGTTG GTTCCAAGTA TTTGCTATTG TGAATAGTGC 128640
CGCAATAAAC ATATGTGTGC ATGTGTCTTT ATAGTAGCAT GATTATAAT TCTTTGGATA 128700
TATACCCAGT AATGGGATCA CTGGGTAAAG TGGTATTTCA AGTCTAGAT CCTTGAGGAG 128760
TCGCCACACT GTCTCCACA GTGGTTGAAC TAATTTACAC TCCCACCATC AGTGATAAAG 128820
CATTCTATT CCTATGTCTC CACATCCTCT CCAGAATCTG TTGTTTCTG ACTTTTAAAT 128880
GATTGCCATT CTAATTGGCC TGAGATGGTA CCTCATTATG GTTTTGATT GCATTTCTCT 128940
GATGACCACT GATGATGAGC ATTTTTTCAT GTGTCTGTTG GCTGCATAAA TGTCTTCTT 129000
TGAGTAGTGT CTGTTTCATAT TGTTTGCCCA TTTTGTATG GGGTTGTTG TTTTTTTCT 129060
TGTAATTTG TTTAGTTCT TTGTAGATTC TGGATATTAG CCCTTTGTCA GATGGGTAGG 129120
TTGCAAAAAT TATCTCCCAT TCTGAGGTT GCCTGTTTAC TCTGATGATA GTTTCTTTTG 129180

FIG. 6.49

CTGTGCAGAA GCTCTTTAGT TTAATTAGAT CCCATTTATC TATTTTGGCT TTTGTTGCCA 129240
TTGCTTTTGG TGTTTTAGAC ATGAAGTCCT TGCCCATACC TATGTCCTGA ATGGTATCGC 129300
CTAGGTTTTTCT TTTATGGTTT TTAGGTCTAA CATTTAAGTC TTTAATCCAT 129360
CTTGAATTAA TTTTGTATA AGGTGTAAGG ATGGTTTCCA GTTTCAGCTT TCTACATATG 129420
GCTGGCCAGT TTTCCAGCA CCATTTATTA AATAGGGAAT CGTTTCCCCA TTTCTTGAGC 129480
TACAGATATT TTGAGTTTGG TTACCACAGT ATTATCTAGT GGAAGTTGAC TTATACAGTA 129540
TGTAATAGGA TAAATATAGG TGTGTAACAG AATATTAAGT GTTCGTGTTT CAAAGCTGAG 129600
GGGAAAATGT TAAAAGTGT CACACACTCT AAAAAGAGAT TAGCTAAAAC TGCTTCATTA 129660
ACCACACTTT GGGGAAACCA GTTCTGAGAT TCTTCTCCAT TACTCTGACA GGTTGGACCC 129720
TCTGGGGAGC AGATCTCAAG ATCAAGTTAT GAGTGCAAGA GGTGTGTTGG GAAGCGATGG 129780
TTGTAAAAGA ATCCTGCAGT AGCACCAGGC ACAAGTCTGT CCAGGGAGAG GAGGACTTCT 129840
ACTCTCTACC AGCATCTCTC CTAAGTCCCC TTAGGGGACG GGGGCAAGGA AGTGCTGGGA 129900
AGGGCAGGGC ATGGTTCCTG GCTAGGACTC CACCCCCCTG GGGCCTGTAC CCACGGACCT 129960
AGGTGAAGAC AGGCACTCCT GCCTTCTCGC CCAACGGTTG CGTTTCCCAA GATCATCCTG 130020
GCCTGCCACG CCCCCATCTA CCTATTAAAC TCCCCACCT TCCCCAAACC CTAGCAGGCA 130080
GACACACATC GGTGGAAGAA GACAGGAGCG GCTGGACATT GAAAGGACGT CGAGAGGAGC 130140
ACACCTGCAC ACCATCGACC AGCGGAACGA GGCAGAGTGT GGCTGGAGCA GTCGGAGGGA 130200
AGCCTGGGCC GCTGACTCCA GGGGAAAACC ATCTCCTTTC TGGCTCCCCC CTCTGCTGGG 130260
AGATACTTTC ACTGAATAAA ACCTTGCACT CATTCTCCAA GCCCACCTGT GATCCGATTC 130320
TTCCTGTACA CCAAGGCAAG AACCTGGGAT ACAGAAAGCC CTCTGTCTT GTGATAAGGT 130380
AGAGGGTCTA ACTGAGCTGG TTAACACAAG CTGCCTATAG ACAGCGAAAC TGAAAGAGCA 130440
CACAATAGCA CACACTCATT GGGGCTTCAG GAGCTGTAAA TATCCACCCC TAGACGCTGC 130500
CATGGGGCGG GAGCCCCACA GCCTGCCCCG CTAGAGGTTT GAGCAGCGGG AACTGAAGA 130560
AGAGAGCCAC ACCCTCATCG CACGTCCTGC GAGGGAGACA AGGGAACTTT TCCGTTTCA 130620
CTTCTGCTTG GCTTGAGCTG GCACTGAAGC ACCCTTTTCC CTCCTCACTG AGGGAGCAGA 130680
GGGGAAAAGC GGTAGAACTA ACAGGCTAAC AATGCTCTC CGAAAATATA TCGTATTTTT 130740
GGATCCCTAG AGATAGGTGA TCACGGCAGC CGCGGAGTGC ATTTGGGTCT CCTTTCAAGA 130800
AAGAACTTGC TGCTCAGCGT TGAAGAATGC AGTTGGCCAA CAGCCTCCAG CTGCTCTGTC 130860
TTCAGCATCT GCCATGGCAT CTGAGCTGAG GTCATGTTCT TCCTGGGAGG TCCCAGCAG 130920
AAGGATCACG TGGAAGCTCC ACAAGCTCCA CAGATGTTCC AGGAGAGGAA TAGGCAGCAT 130980
TTGGAAGACA TATCCTGCCA TAACAGAGGG CATTGCTAG TAGAGACAAC AAACAGCAAC 131040
AGCCAAGTAA ACAACACAC AAGCACAAG CACTTCTCC CATTCCCCCT CATTGATCCT 131100
GTCCGGGTAG AAGCTGGGGA GGAAGTAGAA TAGGGTGAGG CGGGGTGGGG CTGGGGGGCC 131160
TACACCTTCT TCCTTCCCC GCAGGTCCTG TCCCTGGGCC AGGCTTGAAC TAGGGGAATG 131220
GGAAAAGCTG TGAAGTGAAT GAGAATTAGG AGTTTTTATT TAGACTGGAC TTGAATTTTT 131280
TTTTTTTTTT TTTTTTTTTT GAGACAGAGC CTCGCTCTGT CACCCAGGCT GGAGTCCCGT 131340
GGCGCCATCT TGGCTCACTA CAGCCTCTGC CTCCCGGGT CAAGCGATCC TCCCACCACA 131400
GTCTCCTGAG TAGCCGGGAT TACAGGTGCC TGCCACCATG CCCAGCTATT TTTTTTTTTT 131460
TTTGATTTTT TAGTAGAGAC AGGGCGTCAC CGTGTGGCC AGGCTGGTCT CGAACTCCTG 131520
GCCTCAAGTG ATCTGTCCGC CTCGGCCTCC CCAAGTGCTA GGATTATAGG AGTGAGCCAC 131580
CACGCCTGGC CTGGACTTGA ATTTTAAATT CTAATAATG AACTACCACT TAAATTTAA 131640
AAATGACCAA AAAAGCTATG GGATATGCTG ATGTTTGTCT TTGGGGATAA GGAAAAGATA 131700
TCTGGTTGAG CGGCATTGAA AACAGTGTAG GGAGAGAAAA ACTCATTCTT GGCTCACCCCT 131760
TTTGAGTCCC ACTATCTCAA TAATCTGATG TTATATGACA CACACACACA CACACGGAGG 131820

FIG. 6.50

AATCCTGGAA GACTCCATAT CAAGGTGGTG ATGAAGGTGA CCAGTGGGTG ATAGGATTAT 131880
AGGTGTGTGT TTATTTATTT ATTTTAATTA CCTTTTTTTA GAGACAGGGT CTCTGTCATC 131940
CAGGCTGCAG TGCAGTGGTG TGATCATGGC TCACTGCAGT CTTGCACTCC AGGGCTCAAT 132000
CCTCCTGCCT CAGTCTCCTG AGTAGCTGGA GCTGCAGTCA TGCACCAACG TGCCCAACTA 132060
ATTTACTTTA TTTTATTTTT TATTTTTTGT TAAGATGGAA TCTCACTTTA TTGCCTAGGC 132120
TGGTCTTAAA CTCCTGGTTT CAAGCATTCC TCCTACCTCA GCCTCTCAAA GTGCTGGAAT 132180
TACTGCACTT GGCCCTATTA TATTTTTAAA AAATTTCAAT AGTTTTAGGG GTAAAAGTGG 132240
CTTTGGTTAC ATAGATGAAT TGTATAGTGA TGAAGTCTGG ATTTTTAGTG TACCCATCAC 132300
CCAAATAGTG TACATTGTAC CCAATGAGTA GTTTTTCATT CTCACCCCC ACCTGTCCC 132360
CACTTCTGAG TCTCCTGATG TCCATTATAG CACCCTGCTT TTGCGCACTT AGAGCTTACC 132420
TCCCACCTAG AAGTGAGAAC ATGTGGTAGT TGGTTTTCCC TTCCTGAGTT ACTTCACTTA 132480
GGTCAGTGGC CTCCAATTC ATCTGAGTTG CTGCACATAA CATGATTTC A TCTTTTTTTT 132540
GACTGAGTAG TAGTCCATCT CTCTCTCTCA CACACACACA TACACACACA CACACACACA 132600
CACACACACA CACATTTATC CACTCATCCA TTGATGGGCA CTTAGGTTGC TTCTATATCT 132660
TTGCAATTGT GAATTGTGCT CCAATAAACA TACATGTGCA AGTGCTGTTT TTTCTCCCTT 132720
TTATCCTTCT TTTCTCCCT ATGCTTCCAT AGGTACTGAG AAAGAGTCTT TTTTATATAA 132780
TTATTTCTTT TCCTTTGGGA AGATACCCAG TAGTGGGATG GCTTGATCCA ATGGTAGATC 132840
TGTTTTAGT TCTTTGAGAA ATCTCCATAT TATCTCCATA TTGTTTTCCA TAGAGATTGT 132900
ACTAATTAC ATTCCCACCA ACAATGTATG TGTTCATTT TCACTGCATC GGCACCAACA 132960
ACGGTTGTTT TTTGACTTTT TAATAATGGC CATTCTGGCT GGGGTAAGGT GGTATCTCAC 133020
TGTGGTTTTA ACTTGATTT CCCTGATAAT TAGTGATGTT GAGCATTAA GAAATATATT 133080
TGTTGGCCAT TTGTATATCT TCTTTAAGA AATATCTCTT GAAGTTGTTT GCCCACTTTT 133140
TAATGTGATT ATTTGTTTTT TTTTCTTGCT GATTTGTTTG AGTTCCTTGT AGCTTCTGAA 133200
TATTAGTCCT TTGTCAGAGG TATAGTTTGC AAATACTTTC TCCCATTCTG TAGGTTGTCT 133260
CTTTACTCTG TTGGTTATTT CTTTTGCTAT GCAGAAGCTT TTTAGAATAA TTAGGTCCCA 133320
TTTACTTATT TCTGTTATTT TGTTGCATTT GTTTTTGGGG TGTTAGTCAC AAATCTTTG 133380
CCTAGACCAA TGTCCAGAAG AGTTTTTCCT AGGTTTTCTT CTAGAATTTT TATGGTTTCA 133440
GGTCTTAGAT TTATGTCTTT AATCCATCTT GAATTAATTT TTGTATATGG TGAGAGATAG 133500
GAACCCGGTT TCATTCTTTT AACTACATG TGGCTATCCA ATTTTCCCAG CACTGTTTAT 133560
TGAATAGGAT TTCCTTTCCC CAGTGTATGT TTTGTTTGT TTGGCTGAAG ATCAGTTGGT 133620
TGTAGGTATT TGGTTTTATT TCTGGGTCT CTATGCTATT CACTTTTAT ACCGTTTCCA 133680
TGCTGTTTTG ATTACAATAG CCTCGTAGTA TAATTTGAAG TTGGGTAATG TGATGCCTCC 133740
AGATTTGCTC TTTTTTGCT TAGGATTGCT TTGGCTATTT GGACCCCTCT TTGGTCTCAT 133800
ATAAATTTTA GGATTGGTTT TTCTAATTCT GTGAAAAATG ACATTGGTAT TTTGATAAGG 133860
GTTGCACTGA ATCTGTGGAT TGCTTTGGGT AGTATAGTCA TTTTACAAT ATTGATTCTT 133920
CTAATCCATA AGCATGGTAT GTTCTCCAT TTGCTTGTGT CATCTATTAT TTCTTTCATT 133980
AGTGTTTTGT AATTCTCCTT GTAGGGGTCT TTCACCTCCT TGGTTAAGTA TATTCCTATG 134040
TATTTTATTT TTATTTTTTG CAGCTATTGT AAATGGGATT GAGTTCTTGA TTTGATTTTG 134100
AGCTTGGCCA TCATTGGTGT ATAGCAGTGC TAGTGATTG TGTACATTGA TTTTGTAACC 134160
TAACACTACT AAATTCACCT ATCAAATCTG GGAGATTTTT GAGGATTCCT TAGGATTTTC 134220
TAGGTATGAG ATCATATCAT TGGTAGAGGT AGTTTGAGTT TCTCTTTTCC AGTTTGGATG 134280
CCCTTTATTT CTTTCTCTTG CCTGATTGCT CTGACTAGGG CTTCTAGTAC TATGTTGAAT 134340
AGAAATGGTG AAAAGTGGGC ATCCTTGCTT CATTCTAATT TTTAGGGGGA AATGCTTTCA 134400
ACTTTTCCCC ATTCATTTTG ATGTTGGCTG TGAGTTTGT ATAGATGATT CTTACTATTT 134460

FIG. 6.51

TGAGATATAT TCATTTGATG CCTAGTTTGT TGAGGGATT TATCATAAAA GGAGGCTGGA 134520
TTTTATTGAA TGCTTTTCT GCATCTATTA AAATGATTAC GTTTTTCATT TTTAATTCTG 134580
TTTATGTCAT GAATCACATT TATTGACTTA TGTTTATTTG TTGCTTACAT CTACTTTCTA 134640
ATTTTACTAT AATAAACATG TATAATTTTG TTATCAGAAA AGTAAATGTA AAAGTGAGTT 134700
TTAATTTTAA AACTTGGGCC TAAGTCTTCC TGCCTCCCAA GCCCATTCCC TTCCTGATAT 134760
CTGGGGCTTC CCTCCTCAAG CCTGCTCTGC AGGATAAGGG GATACAGTCC ACATGCCTGC 134820
TGCTGGTTTG GCCCATGATA ACCTCCATGG GCAATGTCTG AGCCTCTGCT GTTGAGTTTT 134880
GCTTTACACA CTCCTGGCAA GGAAAGGATG GCCAACATGG CTTGGACATG GGTTGCTGAT 134940
AATTGGTGAT GTCTCATGAC TGGTCTGCC TGGAGGGCTT GCTGTAAGTC CCTGATAGGA 135000
GGAACATGGA CCTGCACAAG AGCAGAACTT ATCTGACACT GAAGAGGACA CTTCAAGAAC 135060
AGATTATCAA AGTCTAGCTC AGGGAGAAAT ATACTTTAGA GCAGAATGAG GAATGGCGAG 135120
GCAGCTGAGC TTAGACACAA GCAGAAGGAA ATCCATGGTG AGGGCACAGG CAAGGAAAGG 135180
GGCTGAGAGA GCATTAGTGG GGGCAGTCAG GGGCAGTGGT CAGGATGCTC GGATGCCAGC 135240
GTGAACAATC GCATCAAGAT TAAACACCAT GAGGATCGTT AGACTTCCTG TCATATGTCT 135300
CCAGGTGGTG CTCCAAATAT CCTAAACCAG ATGACAGCAC CCCTCCACCC TCTGCTGTAT 135360
AAGCACATCT GCTCTCCTAT AATCATTCCC ACATAGCAAT TTATCATTTT TATTGATTTT 135420
TCTTCATTTA ATACACGTAT AAGTGTGTCT TTTATTTTAA AAAATTTGCA TTCCTTTAAT 135480
TGCTTTGGAG ATTGTGCATT TTTCTCTCTG TTGATTACT CTGCCAATAA ACATGTAATC 135540
CTACCATAAG CATGTTTTAC TTGTGTAATC AACCAAAATA AAAAATTTAA AAAGGAATCA 135600
CTGACTATGA ATTAGACATG TGGATAGGCA CCAGGGTTGC AGACATGGCC CACGTTCTTG 135660
CATTAACTTG CACTGTGGCT GGGGCATTGG ATGGGTACAT TAAAAGGATT AAAGTAATAT 135720
AAGGCAGTAT TTATTAAGTG TTGAGTGAGC ACTACAGAAC CCAAGTGCTG AGGGAGTTTC 135780
ATGCAGGAAG AGATCAAGAG TAACACAGAG AAGAAGAATA GATCAATTTA GCGCATTCAT 135840
TTAAAAATTC ACCTTTTGCA TAAGGGGATG TGTCTTTTGT GGGGAGGAGG GGAGTTCCGA 135900
TTGGCAGTTT GTTCTCAGGG AGCTTGAAGA AGAGATCTTG GAGAGGAGAC GCAGAGAAAA 135960
CAAATGAAGA AAATGTCAAA ATGGAAGGGG TTGGCCCGGC TATGCATACC TTAGTTAGCT 136020
TAGGTAGAGT CTAACCTTTT ACAAGTGGTT TCAATAGGTG TGTTTGGTCT GGGTTCTTTG 136080
GGAGGTATCA TAGGAGAATG AAGGCAGGGA GGACGCTTCC AGCACCAAAA TTCAAAGGGA 136140
AATGATTTT ACATGCATAG CATTGTTTTA CTCTCTTTCC ATTTGGAGCA TATCTTAAAA 136200
ATTCCATTTG GAGCATATCT TAAAAAACCC ATTTCTCTGA CAATGGTTCT AAAAGGGGGA 136260
AACATCCTTT GCAACAGAAT CATTCAATCT CTCATTCATC AACCACTGAT TGTGTACTAA 136320
GTGTCAGACC TGATCTCCAT CCTGCCTGGT ATGGCACTAG CTTCTGTCTT GAGACAAGCA 136380
TTGTGATAAA CCATGACCAA AAAAAGGGCA GTTTTATAAA CACAAGTCTG CCAGGCTTTC 136440
AGCAATTCTA AATTTCTTTT TGCAAGTCAG GCTGGAGTTA ATGGCTCTTT CCTGCAGCGG 136500
CGGAGATGAC AGGGCTCTCC CACAGTGCTG AGCAGGCAGT TTGAAAGCCC CACTTCCTGT 136560
CTCTGCATGG GCGAGTGTC ACTGGAAGCC ACTGAGAGGA AGGAGGGAAA CCTCAGAAAC 136620
CGGCCCCTGC CTGGCTGCTT CACCCTAGAA AGCCCAGGCA GAGGAGGGAA AGGTGAAGTG 136680
CTGAAAAAGA ATAAAAAGG GGGAACATGA AAAAGAGCAA GAGCAGGAAG GAGGCAGGGA 136740
CGGGAAAGGA GGGGAAGCAC GGAAACAGCC AATGTCAAGG AGAAGAAAAG ATGGCTGGTG 136800
GAAAGGAGCT TCCAGGAATT GGGACACAGC CCTGTCTTAT TGCAAAAGAT GGAAACCCTG 136860
AAGGAGAACA GGAAGGAAAA AGAAAACAAG TCCGTCTGAG CTGGCAGGGT CCACTTTCTC 136920
ATTCTACAGA TGAGGAAACA GAGGCACAGA GAGGAAGTGG CTTGCCCAAG GGGGCAGATT 136980
CTTGAAAGGA TCATCTGCAC TCTCTCTCCC TTAATGCATT CTTACCTCTT CTTTACTCGT 137040
GAGTCAGTCC TGAAGGACAA GCTGCCTGAA GTCCACACA GATGGGCCTG GGGCAAGCAT 137100

FIG. 6.52

CAAACATCCT GGGGGCCCTG GGTGAGGTTT GCTTTTAAAT TCCAGGTCAG GGAAAGGAAG 137160
GTCTTTAAGT TGTCTGCTCT AAGCTTAGTA ATCCCCCTCA GAGTTATGGG TGCGGTGTCT 137220
GGGGTAGCCG TTGCGTCTCT GGGCAAATAC CCTGGAGAAT GCAGTGTGG TTGTCTGAGC 137280
TGGGGACAGA GTGACAGCAT AGTTGCATGC AGAGCTGGAG GCTCCTGCAG CTGTACAGGT 137340
AAGGTGCTGA AATTCTCCAC CAACCTTCC TCTTTGCCCC CAGCACCACG AAGATAACCC 137400
TCTTTGAATA TGTGGAAGTC TGTTCTCCAA ACTTTCTAAC ATTCTCATGT CAGTCTTAAT 137460
AGATTGAGCT CAGTTACTGC CTCCTCCAGG AAGTCCTCCT TGTCTGCAAA TCGGCTGCCC 137520
ACCATGCCGG CTCACTCATA GTTTTAACTC TGTATCTTTC TAATATGCCT TAGCCCACTC 137580
TGTCAGGATT CCAGTCAGCT TCCTTCTCCT AGACTAGGAG TTGCCTCAGG CCAGGAGGAC 137640
CAGCCTTGTT CATATCTGTA CCCTGCAAAC CTGTCAATGC CCAAACCTGC TCAGTGCTTT 137700
GGAGTATGGA ACCAGCCGTC AATGCAGGAA TGTTACACTC TAAGAGTTCC CAAAGGTAGA 137760
GAGATGAGGG ATGGTGCTG GAAGTGGGAG GTTATTCTAA GGATGGGTAT GGCAGGAAAC 137820
ACAATTATAG TTCAGGGAGT GGAGTGTCCA GGAGTGGGAG GAGAGGAACT GGGAGAAAGA 137880
GCAGAGAGTG AAAGTGAGAG CGGGCACAAA GAAAGGGAAA AAGAGTCAGG GATCAACCAA 137940
AGTGCATGCT TCCTTTTCAG CCCTGCCAGG ATGTGCAGGG CGGCTGCTGT GGACGCGTCA 138000
AGGCTCAGCC TCAAACATGT CTTCTTCCTT GACTTTTGTC TATCATTCTA AAGCTAGGTC 138060
ATTTAAAAAG TTCTTTTGTT TTCTTTCCAC CGATACTCTG ATTTCTGACA TTCGCCAAAA 138120
AGAGGTCAAG ACCCTGGCAT ACCGCCCTAC TAAGATTAAA ATAAATATTA TCCATTGAAA 138180
CTGTTATTTT TTCCTTAACT GTTATTTGTA GAGTTAAAGA TTCCCATGAT CGCGCTGGCT 138240
CTAACATCAT TTTTGGCTCT TTTGAGATCA AATTTGCAAT TTGATGCAAA AATAGCTGTG 138300
ACGCATATGT GTCTGTATGT GTGTGGTTAG GAGATTTTTT ATCATTACAT CTTCTTTTGC 138360
CCTGCCTTTC TGCTTTTCTG TCCTTTTAAT TTGCGGGCTT TTGGCAACCA CAGCACGGGT 138420
CTGGTTTCCT AGGAGTTTCT TTTGTAGGAT CAAACCGCTA GTTGGCTCTT GGCCCTGTGA 138480
TAGGGCCCTG GGCTAACTTA TTGGGAAAAT GTTGCTGTAA CCCCTGCCCA GAGGTGCCTG 138540
TGACATGGGC CGCCATCTTC TCCTCTTCCC TTGGCTTCAG CCCACCTAG AAACCTGAAC 138600
AAACATTTTC CTTGACATTT CATAAAGTGT CAGTGGCTCC TCATTTAGCA AAATACATCC 138660
CAGGGAAGTT CAAAAGTGAA AAAAGGCCGT AACTTCTTCT TCTTCTCAGG GACCTACAGA 138720
AAATATGTGG CACCTCGGCA GCCTGGCCTG CAGCACTCCC CTCCCCATCG GTGAGTCCTG 138780
CTACAGTGGG TCCAGGTGTC TGGACGCCCG GCACGCACGG CTCTCTGCAG ACCTCTGGAC 138840
AGTACCATGG GAGCCGCACA GTCCCTGCCT GTTCTGTCCG GCAGTTCTTG TTTCCAGCA 138900
CCCTGTCTCA GGTGAGAGGT TCCCTCTTCT GCTGGGCTTC TCCTCCCTGC TGTGAACCCC 138960
AAATATCTGA GGCAGGTCAA TTTAGGAACC TTATTTTGCC AAAGTTGAGG ATGTACCCAT 139020
GACACGGCCT CAGGAGGTCC TGAAGACAAG TGCCCGAGGT GATCGCGGCA CAGCTTGTT 139080
TTATACATTT ATACAGACAT CAGTCAATAT ATGTAAGATA AACATTGGTT CGGTCCCGAA 139140
AGGCCGGACA ACTCCAAGTG GAGAGGGGGC TTCCAGTTCA CAGGTAGATA AGAGACAAAA 139200
TGTTGCATTC TTTGAGTTT CTGATTAGCT TTTCCAAAGG AGGCAATCAG ATATGCATTT 139260
ATCTCAGTGA GCAGAGGGGT GACTTGGAAT GGAATGGAAG GCAGTTCTCA GTTTAAATTT 139320
TCCCTTTAGC TTAGTGATTT TGGGGTCCCA AGATTTATTT TCCATTCACT CTGCAGACAG 139380
GGGCTTCTGT GCATCCAGGG AGCCCCCTCCT CACAGAAGGA AGCAGGCCAT TAATGAGACC 139440
CAATCCAGCT TCAACCACCT GGTAACAATT AGGACATCAC TTCTCTGAGC AAGAGCTCCT 139500
GCCTGTCCAT GAGTTATCAA GACATTCCAA TTGTTCTCC ACATCTTTGA CATGAAGACT 139560
TGAGGGGGTC AGATTTTCCA GGGGGCTTGA TGGCATGTTT TCTTCACTGT TCCCTGCCCT 139620
GGTCATCCAA GTGACCCTTG GCAGGGAAGA GGCCCCGAGT TGCAGAATCT CTGTTCTCAC 139680
AAGCCATTGC CAACCCGGAG AGTGGCTTTG CCACTATTCC TAGCATGTTG TTGGCTATTT 139740

FIG. 6.53

CAGGAATGGG AGTATTTGAC TTTTCCCTTT GCAGTGATTG CTGCAAGGAG AGGAATTGAG 139800
AGACTCAAGT CCCTGAGATA AATATTTATC AACTATTACT GAAAGGGAGT ATGTCAAAGA 139860
AAAAATGTGG AGAAACTTCA GCTTGAACAC ATAGTTTAAA TCCAGCTTGG GTGTACTCCA 139920
GTGGGCATGG ATGTATTACT GTTTTGCAGT GCATTCTTCT ATGATCAATA CACAGAAGCA 139980
AACAGGCCAC GTGGGTAAAC AGTAATTTTC ATTTACCAGG GTGAATATGG AAGTCCTCTT 140040
GTTTCCATGT CATGATGAAG GAAAGCAAGG ACCATCTTTT GCCAAGGAAC AGTGGCTGTG 140100
GGGGAAGTGA GGAGATGGAA GGACAAGGCA GTCAAAAGCT TTGGAACAAC TCTTTTTTTG 140160
AGATGGAGTT TTGCTCTTGT TGTCCAGGCT GGAGTGCAAT GGCACGACCT CGGCTCACCA 140220
CAACCGCTGC CTCCCAGGTT CAAGTGATTG TCCTGCCTCA GCCTCCCGAG TAGCTGGGAT 140280
TGCAGGTATG CTCCACCATG CCTGGCTAAT TTTGTATTTT TAATAGAGAC GGGATTCTCT 140340
CACGTTGGTC AGCTGGTCTT GAACTCCCGA CCTCAGGTGA TCCACCTGCC TCGGCCTCCC 140400
AAAGTGCTGG GATTACAGGC ATGAGCCACC ATACCCGGCC CTTTTTTGGA ATAATTTTAT 140460
AGGTTTTCAA ACTATTACAC TTACCTTTTT ATATAAGAGA CAGGACATAG TCACTGAACA 140520
ATCACTCCAG ATTTTAAGTA AGTCCAGGAT GGGATGACAA TGGAACAACC ATGAAATGAA 140580
AGGAAGAATG TGTCAGTGGT ATGTCCACAC GTCTCCAAAT CTCTCACCTC TGTCAGCTGC 140640
AAACAGAGCC TGAAATAAAT GTTTCCTCTG TGCACAGCCT CCACAACTTC CTCCCTCCAC 140700
GTTTCTCACT CACTCCTCTC CAGCACTTCT CTCCGGGTTT TGCTTACAAA CTTGAAACCG 140760
GCTATGCAAA AATTATAACT GTGGAAATTA TGACAGTGAA AGAGATCAGA CCTAACCGAC 140820
TCCATCTTGC TTCTAACCTT TAAGCTGTCC TTGTTTCAATTT TTGGGCTGAA CTAAGTTTGG 140880
GAAGGAATTC AGTTCATGGT AGAACTCTGA AACAAAATTG ATAATAGCCC TTTCTGAAA 140940
AGACCCCTT CTGCTGCTGG GACAAGTCTG CCATTGTAGG ACTAACAAT TAACTACAAG 141000
ATTAGAAAT AAGGTTTAGG GTTCATGCAG CCTCCAGTTC CAAGAGTCTA AACCTCCCCA 141060
AATTGCTCCT GGGGATAACA TCACTGTTGT AAAAGCTAAG ACCAGTGCTT GAGATATTTT 141120
GTAGACCCTG CTCTGGATGG ATCAGCTGAC ACCATCCAGA CTGGTAATTT GGCTCAACCA 141180
GCTCTGCCAT CCCACCCAGG AACAGAAAAA TACTCACTTC ATCACCCCAT GAGTCCATCT 141240
CTAACCTGAC CAATCAGCAC TCCCTACTTC CCAGGCCCTT ACTCGCCAAA TCTGCCTTTG 141300
GAGGCAGATA ACAACTTATC TTTAAAAACT CTGATCCCTG AATGCTCAGG AGACTGATTT 141360
GAGTAATAAT AAAACTCCGG CTCTGCATGA ATTACTCCTT TTCCATTGCA ATTCTCTTGT 141420
CTTGATAAAT TGGTTCTGTC TAGGCAGCCA GCAAGGCGAA CCCTTTGGGC GGTTACAAAC 141480
TCATCCTCTG TGGAAGAGTA GGAGTTCATG GAGAAATTGG TTGCAAATTA CAAAATTTTA 141540
TTGTAAGGTC AACTTGTCCT AGTGTCCGTC TGTGCAGCGA AGGGCCCTG CATGGTTTAG 141600
TGATTGCAAG TTGAGCCTCT AGGGTCAGGT TGTCTAGGTT TCCATCCCAG CTCATTCACT 141660
TATTATCTGT GTGTTCTTGA GCAAGCTCCT TAATCAATTG AGGCTTTGTC CTTCTGTTTG 141720
TATAATGATG AGAATAATAA CCTCCACAAT AACCTCATCA TAAGGTTGTT GTGAAGATGG 141780
ATCAGATAAT ATATATGTAG AGTGCTTATA ACAGTGCTG GCACATAAAA AATGCTCAAA 141840
AATCTTAAGT GTTATTAATA ATAACTGAC ATATATTTCT TGAGCAGGGT GGTGGTAAAT 141900
GGGTGTTCTT TTTATTAAGC TTTAAAGTGT GCATAGATCA TATTAATTCT TTTTATGCAT 141960
ATGATATATT GCACATGCAT GAAAATACAT GCATTAAAAA TAAATGAGCA TTTATGAGAT 142020
TTAGTTTAGC AGTCACATGT CCCAGGATTA CAAGCCAGCA ATAATGGGTT GGAAAACATT 142080
CCAACCCATT CCAACCATTG GAAAACATTC CAACCCATCA CTGGACCCAT GTGCCAAACA 142140
ATGGAACCGC CCACAGGTTT TCATTCTTGG TTAATAAAT ATGATTATTA CGGGAATAAT 142200
ACTGATTCCC TAAGAATTAA TATCTGAGCA AGTTTCTTTT TTTTCTGTC TTCTTGGAAG 142260
ATCAGCAGGT TCTAGATTCA ATGGAGTCAC TAGGATTGAG CCACCAGTAT ACGCCAGTCC 142320
TCTCCAGAAC GGCCACCTGG TGGTGGGCAC TAAGGCAGTC TCAGATGAGG ACTGATTGAC 142380

FIG. 6.54

TTTTGTGTGA ACTCAAACCTG CCAAAGTCCC TCCCTCACCT TGCAAACCTC AAAGCACAAC 142440
TTTCAAAGCA CTACTTTCTT TCTTGGCTCT CAATTCTCTG CCTAGAAAAA GGGAGGTGTT 142500
GGCAAGGATG TTTGTTTAGT TCTGGGCATC AGTCAATGGT ACCCAGATCT TGCTGAACAG 142560
AAAAGACACA GATTGTGTTT TCTGAGGCAG TTGGTAGTGC TTATTGCTTA TTGCTCTCAG 142620
GGGCTTCTGC AGCAGTAGAA GGGCCCTCTT CCCCTGCCAT GCCACACTGA GAGGAGCATC 142680
CTTGAGTCA TGGTTGGAAT CTGTTTTTGT TATGCTAGTC CTCTCCGCA TGCTAGCTGT 142740
TGCATTGCAG GGATATGTGT ACCTGTTTAT CTTCTCCACT AGGCTCTAAG AAGCCAGGTT 142800
TCTTAAAGGA AGGAAGCTGA TCTTGTGTTAT CTTGAAGTCC TCACAGTGAC ATTGCTCAGT 142860
CAATGTTGAG TGTATGAATG AATAAACGGG AACCATCACG AAAAAGCCGA AAATACAGTG 142920
GAAAGACTGG ATCATAAAAT CTTCTAAGCA AATTTTTTTT CCTCTTACAC TCCATTCCA 142980
AATAGATAAA GTATTTTTTA AAATCCTATC AGAATATTCT AACACACTGA GTTGACAGAA 143040
TAGAGATTTT TAAATGCAGT GTCATTTGGC CAGCCATTG TGAGAATTTA TAAATGTTTC 143100
AGTAGGTTGA AAACACTATA AAAGCAAGGA CTATGTTTAT ACCCAACAGC TGGCACTTAG 143160
TATGAATGCT AAATGAAACA TTCTCTTCTC TTTCAAGAGT CAGTCCAACC AGTGACCCTG 143220
ACAAGAAGGA AGGCACATTT AACTCAATTT AATGAAGTCT TATAGAGCAT CTCCTTCTCC 143280
AAGTGCTTTG CTAAGGATGG GGTAAAAACA TGAATAAGTC TTGGATTCTG TCCTTCAGGA 143340
ATTTTCAGTC TTTGGAGGCA GATACATTG CACCCAATA TTATCCTAGG CAGAGTGTGA 143400
TAAGTACGAT AATAGCAGTA AAAGCTCTAA GTTAGGCAGG AGAGGAGGAG CTCGTTAAAG 143460
CTTATGGGGC CTGGGAGGCT TTCGGCGGAG TAACTCCAG GGGGACAGCT AGGCATCTGG 143520
CTGCTGGAAT TGGGAGGAGG ATCATTTTAA GTGGCTACAA CTCTGGGTGC ACAGGACTAG 143580
AGGGTGAGGG CCAAGATGGG AAATTGTGGC AGCCATCTTC CACACTGGGC GCCCGCCGAC 143640
CCTTGCTTCC TGGTATTCAT ATTATTGTGT AGTGTCCTCC AACATTGTAT CAGGGTTGGC 143700
CTGTGTGACC AATTGCATAT GGTGGGAATG ATGGTGTGTG ACTTCTAAGA CCAGTTCATA 143760
GAAGATGTGG CCAATTCCTT TACTGTCTTT TTTTGGCA GGGGAGTGCC GAGTTTCACC 143820
CTTGTCGCCC AGGCTGGAGT GCAATGGTGC GATCTCTGCT CACTGCAACC TCTGCCTCCC 143880
AGGTTCAAGT GATTCTCCTG CCTCAGCCTC CCAACTAGCT GTGATTACAG GTATGCGCCA 143940
CCATGCCTGG CTAATTTTGT ATTTTGTAGTA GAGACGGGGT GAGATCAATG AGGCAGTCAA 144000
TTGGCCAGCC TGGTTTGAAT CTCCTGACCT CAGGTGATCC ACCCGCCTCG GCCTCCCAA 144060
GTGCTGGGAT TACAGGCATG CGCCAACCGC GCCTGGCCCT TACTGTCCTT TGGATCAGCT 144120
GCTCTGGGGC TAGGTCAATC CTTTATGTGA CTGCAGCCCC AGCCAACATC TGGACTGAAA 144180
CCCATGAGAC ACCCTGAGCC AAAAAAGCCC AGCTAAGACT TCCTGCATTT CTGACCCACA 144240
GAAACTGAGA AAAGAAATGT TTTGTTGTTG CTTTAAGCCA CTGACTTCTG GGGTCATTTG 144300
TTTTGCAGAA ATAGATAGCA GATACAGAAA AGCAGGCTGG TGGAACAGTG TGGGAAACAC 144360
CTTGATTTTC AGGGAGTTGC ACTTTGTTTA TGTGCAATGG TGCACTGTTT TTAGAAAGAC 144420
ACAAAGATGA TAATACTGGT GATGGGCATA ATACGGGTTG TCAAGAGGAG TGAAGGAGGC 144480
GGGGATAATT TAAGAGGCCA CAGCAGTAGT GTGGCAAGAG GTAATGAGGG AATTGAACCT 144540
GGTGGGAATG GGTGAGATCA ACGAGGCAGT CAATATGGGC AGTGAGTGTG AAGGAGCTGC 144600
GAAGGATGAT TCTTTGTTT TGAGCTTAGG AACATGAGAG AACCAAGATC TCATTTATCC 144660
AAAGAGGAAA CACAGAAGTG AGCCCCTGTT TGGGGGCAGG GCTGGGTAGG AGGAAAAGAG 144720
TGGAGACGTC TATCTCCCCA GGAAGAGAGC CCCCTGCTTC CAGATCCCAG TGGATGGCAG 144780
GGCACTCGGC TCATTCACAG ACTGGGCTCG TTGAGAAACC TTTCCCTGGA GGGCAGGGCT 144840
GCTCTGTTTC ACAGCCCATA TCCCTCATGG CCAAGTGTTT CTCGAGTGAC AGTCTCTGCC 144900
ATCAATATTT TTAGCATGTG GTCTTTTCTA GACTAAAGAG TGGCATCCAT CTCCTGAAAC 144960
TCCTTCCCCA GCTGACAGCT GGTGACCCGT GGAGGAGGGA GCTTCAGGGA GCCTGATGGG 145020

FIG. 6.55

CGAGAGTCTG TTCCAATGCC AATCCATTGG AAGAGATGAA GTCAGACCCG AGTTTGATAG 145080
AAAGCCTACT TCCTCCCTTG TATCCAGCTG TGGAGACCTA CCAACATCAA TGCAAACCAG 145140
AAGCTAACAC CCAGTTCATA TATCCCAAGT GGAAGGAAGC TTCTCGTGGA ATTGTCTTAC 145200
ATGACAGTAA CATAAATCCT GAAGGTAATA CTTGGCCAGG TAATGTTAGA AAAGAACCCG 145260
AACATAGGCA TTGCTATTAT AGATCCTAGG ATAGGCCTGA GCAAAAACTG TCTGGGATTC 145320
ATAACATGCT TCGTTGCAAT CTGATAGAGG GAGTGAGATC CACTCCAAAT GGAGTCTGAT 145380
TTGGGGCAAA GCAAAGAGTA TGAAGGAAA CTTGAGAAAAG GGGGACAGCT TCTCAAATGG 145440
AGTCTGGCCA CAGCTGGGGC TGGAAAAGAG ACATGACTGC GCTTGACAGAG TGGTGAGAAT 145500
TTGCTGCTAG AATTTTTAAG TTGTGTGTTT TCATTTTTAT GATAATGTAA ACTGAGATAA 145560
GCATATTCTC TGCTATCCCA ATGAGCCCCT CCTCTAGGAG GACTACCTTG CCACCTTATC 145620
CATAAATGTG TTTATAAATT ATTTTGATGC CAGCTGGTAT TTTTAAAAA GTGGTTTTGG 145680
ACTCACAAAA AAAACCATGA TGGATTTAAT ACATAACAAA GCATTTGTGT CAAGTGAAGG 145740
CCAAGTAACA TCTTAGCGTC CTGTGTGAGC GAAGGTGTCG TGGCAGTTCA AACAAGAATG 145800
CCGATGAAGC TGCCCAGGAT GGCCAAGGCC ACCTTGGTGT GTTTGAGGGG AATTAGAGTT 145860
TAGAAAAAAA AAAAAGGCA CCTGACACTC TGAACAAATG TGGTTACCTG GAATTTTGGG 145920
GTTTTGAAGC TTTGCATTTA ATTTGCAGCT TATGGCCTGA AGGAAAAGAC AGGTGAAATG 145980
CATATCCTGG GATGAGTCAC CTGGAGGAGA GGGCTGGGAA GGGGCTGAGC TGCACATGCT 146040
CAGATCTTCT CCCAGGCTTA TCGACCCAGT GAGTCAAGTC TTCTTCCAAC GGGATAGAGT 146100
GTGAGAGAGA GCAGGGAACA GAAGCCAGAG TCTCTGTAA ATTTCTCGGT ACATTTCTGT 146160
TAGAGAATGG AAGTTTCTCT ATCGTAGGAG ACCTTGAGAG CCTGGGATAG AAATTACCCC 146220
TTTGTCTATG ATTTTCTCC CAGAAATAGC ATGGCCACTG TCACTGCTAA GCTGGAGTAT 146280
CATGAGCACA ATTTCTCTCA CTTTCTATAC CCATGCCTTT CTAGGAGATT GGTGGCTCCA 146340
TCAAAAAGGA GTTAAAAAGA AGCAGCACTA TTTTGTGGAA TACAATCATC ACCATTATCA 146400
CCATCAGCAC CACCAACCAG CACCACCATT ATCAAAGCA TTCACCTGGT GTCTGCCTTA 146460
CAAAGTCAA ACTGCAGTAG GTATTTGTAA TAGAATGTTT CCTTTCCCCC TTGGGATCTG 146520
CAGAAAAGCT GGAGAATGTT TTGGTATCAA CACACTAGGT TGCATTGCTA ATCATGTGAT 146580
GGCCCCATGA CAGTCTCTGT TGGCTGGTGT AGTTCAGGTG GACGACTGCA GGATTTTGT 146640
CTTGAGCCT CAGTTCTGAC TGGGCTTGGG GTGTAAAAGG TTTGGGAGCC AGATGACAAG 146700
AGTATTTGAT GGGTAGAATA ATGGGTTCAT CAAAAGATC ACCAGAATGG TTATTAAATA 146760
GTACAAAGGA GGAATTTACT GGTAATACCA GTTTGCAAAC AGAGAAGAGA GTCTCCAATG 146820
TGGACTGAAA GTGCTCTCTC TTTGAAGAGG GGAAGGACAG ATTGGGTTTT ATGCCTCACA 146880
GGACTGGTAC CACACATATT CAGCAGGTTT TTGGGGAAAA TCTATACATA TTTATAAGGT 146940
GAGCTGATGC CTGCATAATA GATAAACATA TATGTAACAT ACTTTTCATA TTCATTTTGG 147000
GACTGGGTTT TGGCACTAAA ATTTGTGGAA TTTGGCTCTT TATGTTAAAA GGTGAACTAG 147060
AGGACACAAA GACGGTTTGT GTGCACCCTC TATAAAGTGG CTGAACTGG CTTAAGGTCT 147120
GCAACTGCTT ATCCAAAAAG AATGTTTGTG AGGCCAGGCC TCTGTCCAGT CAGAGTTGTA 147180
GTGGTCCAGG TTGTAAATCA AAGTTTATAG CTCTTTTGT TAGAGAGTTC AGCTGTAGGA 147240
ATTTAGAAAT TTGCCATGCC TGCCAGGCCC TGAACCTTG ACCCATAGGT AACTTTATTT 147300
CCTTAACCTT AGGGTCAGTC TTAGTTGATA TGGGGCATCT ATTCTGGTAT CTCAGATCCT 147360
ATGGTCAAGA GAAAAGATCC TCCACAAGAG GGTCTATGT GGCTGCAAAA ACTGCTCTGA 147420
GCTAAATCCA CTCAAAATCA CTGCAGGATG TCACTACTAG AAAATAGGGC AGGGATAGGG 147480
ATCCCCTTCC CATGCTGCCA GAAAATGCCT GATAGCTTAC CTCCCCCGGC CCTTGAGGCT 147540
CCCTTGAAT AGGCACATGC AATCCCATCT CCACCCAATA GAGCTTGTCCT TAGAGCTCAG 147600
TTTTTCCCA TAGTTTTCCC ACCCACTTGC ACCAGAAAAT CTAATAAAGT CATGTGATTA 147660

FIG. 6.56

ATACAATTCA TTTTATCACG CTTCTGAAGA TTTAAGAGAG AGCGGTCACA TTGGATTCCA 147720
CAGTACCGAC CTTCTGACGA TTCTTCATTT CACCTTTATC TATTTTTATT TTTATTTTAT 147780
TTTTTTTTCG AGACGGGGTC TCACTCTGTC ACCCAGGCTG GAGTGCAGTG GGGCAATTAC 147840
GGCTCACTGC AACCTCTGCC TTCTGTGCTC AAGCAATCCT CCCACCTCAG CCTCCCAAGT 147900
AGCTGGGATC ATAGGTGCAC ATCACCAAGC CTGGCTAATT TTTTGTATTT TTGGTAGAGA 147960
TGGGGTTTCA CCATGTTGCC CAGGCTGGTC TTGAACCTCT GAGCTCAAGT GATCTGCCCA 148020
CCATAGCCTC CCAAAGTGCT GGGATTACTC ACGTGAGCCA CCTCGCCTGG TCCCTTTCAC 148080
CTTTATTATC TTTGCCTTTA ACTCTAGTGC TTCCTCCCTG AATCAGTTAA GGATTGCATT 148140
TGGCTGCATT AACAGAAACC TGACTGCAGA AGCTTAACCA AATAGGGTAG TTTTAAAGA 148200
GAGATTGCTT ACATCACGCA AATTGCACAA ATTTAAAGTG CATAGTTCAA TGAGTTTTGA 148260
CAAATGTAGA ATAACATAGC TATATAAAAC CATTCCATCA AAAAAATTTT ATCACCATAG 148320
GAAATTGTGT CCTGTCCCTT TCTGTCAAT CCCAACTCCT CCCACAAGG CAACCTTCAT 148380
TCTCATTTCT CTCACCATAG CTTAGTTTTA CATGTTTCTA TAATACAGCA TCATATAAAT 148440
GGAATAATAC AGAATGCAAT CTTTGTATG AAGCTTCCTT TGGCTCAATG TAATGTTTAT 148500
GAGATTCATC CATGTTATTG AATGTATCAG TAGTGTTCCT ATTTATATTT CCTAGTGTTT 148560
TATTGAATAA ATATACTACA ATTTGTTTAT CCACTTATTT GTTGATGAAC ATTTGGACCG 148620
TTGGCAATTT TTGCCTATTA TGCATAAAGC TGTTAAAAAA CATTCTTGTA CAAGTCTTTC 148680
ATTTCATATG TTTTCTTTT TCTGAGGTAA ATAACACAA GTAGAATTGT TGGGTAATAA 148740
ATAGGCATCC ATCTAATATT ATAAGCAACT GCACAACAGT TTTCAACGT GGCTGTACTA 148800
TTTCACTCTC CCAATAGCAA CGTATGTGTT TTCCAGCTAC TCCACATGCT CACTGGCATT 148860
TCCTGTTGCC AGTTTAAACA TTTCAGCCAT TCCAGTGGAT ATGAAATCTC TCTGGCTATA 148920
ATAATTGTAT TTCTCTGATG ACTAATTATG TCAAGCCCCT TTTCAAATGC TTATCAGCCA 148980
CTTCTATACT GTCCTCTGTG ACATGTCCGT TCAATCTTTT TGCTCATTCT TAAAAACAT 149040
TGGGTTGTTT GTCTTTTCT TAGTTTGTCT TTTGCTTTTC ATTTATAGGA GTACATATCT 149100
TCGGAATACA AGTCCTTTGT CAGATAAATG TATTGTGAAT AATTTTCTCC TAGTTTGTGG 149160
TTTGCCTTT CACATTCTTA ATATCTTTTG ATGAGTGGAA ACTAACTTTC AAATTATGTT 149220
CAGTAGATTA ACTTGTTTTT GTTTTGTTTT GTTTTGTTTT TTGTTTTTAA CACTGGGTCT 149280
CACTTGTTGC CCAGGCTGGA GTGTAGTGGT GCCATCATGG CCACTGCAA CCTCTGCCTC 149340
CTGGACTCAA GGGATCCTCC TGCCTCAGCC TCCCAAGTAG CTGGGACCAC AAGCACGCAC 149400
CACTACACTT GGCTACTTTT TTATATTTT GGTAGACACA GGATTTCGCC ATGTTGCTCA 149460
GGCTGGTCTG GAGCTCCTGA GCTCAAGCGA TTCACCCACC TCAGCCTACC AAAGTGCTGG 149520
GATTACAGGC GTGAGCCACC ACGCCCAGTC GAGTAGATCA AGTTTAAATT TTATGGCCAG 149580
TAGAGATCTA TTTCAAGGCT CTCTATTTTG TTCTGTTGCT CTATTTATCT ACCTTTATGC 149640
CAATTTTCTT CTCTTTTGAT TCAGATAGGG TTATAATAAT AATTATTTT TCCAGGGATT 149700
AGATGGACCA GGGCTGGTGA AGTTGTTCAA GGGAGTGATC AAGAGCCTGG CTCCTTTCAT 149760
CCTTCTGTTT CATCTCCTTT GGCTCATGGA TTTTGTTCCT CAAGTGGCAA GATGGCGCCT 149820
CCACCTTTGG TATCCTATTT TAGTTCCTGG CAGAAAGAAA GGAACAGGCT AATGGCCCTG 149880
ATGAGTCTAC CCCCTTTTAA CAGGAGAAAA TTTAAAAAAC AAAAACCATG AAACCCTTTC 149940
CCAGAGGCAA CAACCAGAAT TCCATTTATC TTTCATTGAC CAGAACAGAC CACATGGTCA 150000
CTGGTGGTGG CAATGGAGAC TGGGGAGATG AATATTTTAA AGGTGGCATA TTCCAGAAGA 150060
ACACTGTGCA CTGATTGCAT TAATGAACCC ATTAATGTGC CAAGGGGAGG TTTACCTATG 150120
AGCATGGGCA AATTAGAACC CACTCTTGGA GCTGCAGGTG AGCCAATCCC ACCTAAACAG 150180
TGTGGATGCT ACAAGATGGG GAAGTAAATT GATTCTATTC CATACCCTAA CCTCTCTCCA 150240
AGATGTATTC TAAAAATAGA AGAGGAAGA CAGAAGAAAA CATCCAGAAT ATATTTTAT 150300

FIG. 6.57

TGTCTTTTAC TTCTTCAGTG CATTTTAGAT CAGTGCTTCT CAATCTGGCA AGGGGCATGC 150360
AGGAGGATGT GAGTTTTATC AGGAAACTA CACAACCCCC CAACCACAAT GCTACCCCCA 150420
CTCCTGTGGA CCTTCTTTAA GAGAGACTCA CTATTATAGA TGGAGTTGAT ACGATTTTAA 150480
GAGAGGCCAT ATATTATTG CTTTCTGTCT TGAAAACTT GTGATTTTTC TGTATTGTGC 150540
TACTGCCAAA GAGAATAGAA ACCTGACTGA GGTGTCAATG TTTATGTAAC TGATTTCATG 150600
TACTTTCTGT AGTTCTACCA TTTCTGATGG TTAATAAFTT CTTGTGTGTG TGCAGTTGGG 150660
GAGTGTGTCC TCCTCCTTCT GCTCTTATAC CACACATTAG CACATCAAAA TGCTCTAATC 150720
TTTGTATGAT TATGTGGCAT GTGGTGATGC AGCCTCACAG TGGAAAACT TCTCTTGGGC 150780
CATTGCAAAT GTAACATTTC TTTCAATCAG ATAGTGCCAT TAAGGATTTC ATTATGGCCG 150840
TCACATCCTG TGACATCTCT AACATGCAG CATTAGGGCC TAAGTGCAGC CCTGCAGGTA 150900
GAGTTGCCAG GTTTAACAAA TAAAAATTAC ACGCTGGCCA GCGGGGGTGG CTCATGCCTG 150960
TAATCCCAGC ACTTTGGGAG GCTGAGGCAG GTGGATCATT TGAGGTCAGG AGTTCGAAAC 151020
CAGCCTGGCC AACATGGTGA AACCCCATCT CTAATAAAAA TACAAAAATT AGCTGGGCAT 151080
GGTGGCAAAT GCCTGTAATC CTAGCTACTT GCGAGGCTGA GGCAGGAGAA TCACTTGAGC 151140
CCTGGAGGCG GGGGTTGCAG TGAGCAGAGA TCACACCATT GCACTCCAGC CTGGGTGGCA 151200
GAGCGAGATT CTGTCTAAAA AACAAACCCG TATTTGGGGC ATGCTGATAC TAAAAAATTA 151260
TTCATTGTTT GTCTGAAATT AAAATTTAAA TTGGGGGCCC TGTATTTTAC TGGGCAACCC 151320
ATTTGCAATA TCAGCAACAA TCTCTTATTC AGACCACTGA TTAAGTGTGC AAAATTTGAA 151380
TCTCTGAACA GTACCTATGT CCTTGATATC TTAAATTAAT GAGTGTCTTA GACACTCAAA 151440
GCAGGAGGAA GCATTATGGC AGATGTTTGA GCCCCAGAGA TGTCCATGAG CACAGCATAG 151500
AGCTCAGAGC CTCTTTTATT ATTTGCTTCA CGACAGAGCA AAGGACTGCA GCAGGTTGAC 151560
TGATATAAAA GTTTTACCAT GTCTCACAGC AGGCCTTTC TCAAGTTTCC AGTAAGGATA 151620
TTGTATCATT TCTTGCCTGC AGTACTTGTA AATCCACTTA CACTGCCTGC TGTTGAGTCA 151680
TTTGTTCGT CTTGAGTAGC ATGTCATCCT TGTCCTAGA AGATAGTGAG TTTAGAGACA 151740
GTAGCCAAGC AACAGCAGAG CAGCCTCAAC CAAAACGATT TTCCATTTTG GTGGGATGAA 151800
TTGAAACACA AGCATCTTCT ATCCAGGGGA GATTTGGGGA TCATAAAGAA TCAATCTGAG 151860
CTGGTACCAC CATATTGGCT GCTGCATTTT CTAGAGTTGC CGTAACTAGT CTCACAAGCT 151920
GGGAGGCTTT ACACAACAGA CATGTATTGT CTCATAGTTC TGGATGCTAG AAATCTGGAA 151980
TCAAGGCTCC AGGGGAGAAG CTGCTCCATG GTTTTCTCTT AGCTTCTGGT GTTGCCAGCA 152040
ATCCCTGGTG TTCCTTGGCC CGCAGGCGGA TCACTCCCAT CTCTGCCTCC ATTGTCACAC 152100
GGCATTTTCC CAGTGTGCCT GACTCTGTGT TTCTTCTCAT AAGAACATCG GTCATATTGG 152160
ATTACAGGCC CGTGCTACTC CATTATGACC TCATCTTAAC TTAACAATT ACATCTGCAG 152220
TGATCCTGTT TGCAAATAAG GTCACATTCT GAGGTTCCAG GAATTAGAAC ATAGACATAT 152280
CTTTTGGGAA CAAAATTCCA GTGATAACAG TTTCGGAGAC AGACTAGTCC TGGAGTTTGT 152340
AAGGTGAGCC AGGACCAAGG TGCCAGGATT CTCATTTTGT AAGGTCCAGG AACAAAGTGA 152400
TGTTAATAGA AAGAACATGT TTTTGTGTGT TTATTTGTTT TTGAGACAGT CTCACTCCAT 152460
CACCCAGGCT GGAATGCAGT GGTACAATCT CGGCTCACTG CCGCTGCCAT CTCCCAGGTT 152520
CAAGCGATTC TCCTGCCTCA GCCTCCTAAG TAGCTGGAAT TACAGGTGTG TCCCACCATG 152580
CCCAGCTAAT TTTTGTATAT TTGTGTGTGT GTGTGTGTGT ATATATATAC ACACACACAT 152640
ACATACATAT ATATACATAC ATATATATAT ACACACACAC ACATATATAT ATATATAAAA 152700
TATATATTTT TTTTAGTAGA GACTGGGTTT CACCATGTTG CCCAGGCTGG TCTCGAACTC 152760
CTGCGCTCAA GTGATCCACC TGTCTTGAC TCCCTAAGTG GTGGGACTAC AGGCACAAAC 152820
CACCACGCCC AGACAGAAGG AATATGTTTC CTTCCAGTCT CACTTGACTG GCTGCTTCCC 152880
TAGATAACAA CAGAGGATGT CTGTTGCAGT TCTCATTGCT GGGGAGTCTA AACTGGAATA 152940

FIG. 6.58

AAACACCCAC TATCTCCATC AGGCTTGCAC TAGAGCCCAG CTCTAGCTGG AGAGAAAGAA 153000
GCTAACCCGC ACAGACACAG GACTGTAGGC AGGGAGCATC CGGGGGTATT TGGGTCCTGG 153060
CTCTGATGTG CCTAAGGCCA ACTTCTCTCT GGCCATGCTG GCGTGCATGA GCTCACTAAT 153120
CTTCCTTTTT GCCTTCCATT TTCTCCAATC CTGACTTAGC AAAGGTTGGG CAAAAGAGAC 153180
TCTGTGTGAG TTCGAGCAA GCCTGAGATG CTGGATTTTC CAAGATACGA GAAGGGGCTG 153240
GGGGCTGGGT GAACTGGTGG TGGAGGAGGG AAGGATTAAT TTCCAAGGA GGGGAAGGGG 153300
CCAGGACATC AGGCCCCGGG GACTTTGAAG AGAGGGTCGT GGGTAGGAGG TAGATCAAGT 153360
GGAGTGACAC AAAGGTCAGG AAAGAGGAAG TGTCCACACT GTCCTTCGAC AGACTTGAGT 153420
CTATGGGACT TCCTCCCTGC ACGGTACAAG GAAATGAGTA AGTGAGATAA TGTTGTAAGT 153480
TCTGGCCCTC TGACATTGCA CTGCCCCGAT GTCACAGTTG GAAACTGTAC CTGCCCCCAT 153540
CCTTGTCTGG GGTGTGTTTG GTCTGGGGAG GGCTGGTGAA GCAAGAGGTA CTCAGAAAAA 153600
GGACAGAAAT TGCTTCCTAT TATCTGGGCA TTTGGAGGTG AAGGGGTCAC AGCTCTGGCA 153660
AAGATGGGGT TGAAAGGGCC CGGACTCCAG GGAGGGGCAG CTCTGCATGG CCTGATTCTT 153720
GCACCCACCC TTTGCCCCCT CACACCTCCT CTCATCTCCC GTTTTTGAAG AGGAGGACCC 153780
TGTCACATCT GGACAATTCT GCAAGAACTC TGTAGAACTG ACTTCACTGT GAACCAGGCT 153840
CCAGAAGTCA ACAGAAACAA AAATGCTCAC ATTTAATCAC GATGCTCCCT GGCATACACA 153900
GAAGACTCTG AAAACTTCTG AATTTGGGAA ATCCTTTGGC ACCTTGGGGC ACATTGGGAA 153960
CATAAGCCAT CAGTGCTGGT GTGTGTGTGT GTGCGCGCAC ACGCGCATGT GTGTGCATCT 154020
TCTACCATGC CTCCTACAAA TTTGACCTGG GCCCAGGGCC ATGTTCCGGT GTTTTAAAGA 154080
ACCGAGGCTC CCAGAAGCAG TATTGGGCAG CTAGAGTGGC CCCAGGATCT ATATCAAAGT 154140
CTACCTGTTT CTGAACCAA TTTCTTCTAG AATTTTATTC CATAAATCTG AATTATGGTG 154200
TCAGACTCCT AGCATACACT AAAGGAACTC TCTGCCTTGC ATTAAATAAC AGGAGTTACC 154260
CCTGGAGGTA ACTCCTAGCC CTGGCTCTTT AGAGAACAGA TGCCGAATAG GCATTAGGGG 154320
ATGTGATGGA TGTGCTAACT TTCAAAAAA AAAAAAAAAA AAGGCCTGAG CTGAGTGCTC 154380
AGAGATTAC AAAAAGCTGA CAGCATCTCT CTGTTCCATT GGAAGCTGGG TGATCCTTTC 154440
TACTCTTCC TGAGAAAGGC AGTTGGGCAG GAAAAAGCTG TATCTCTGTC CTCACTGAGA 154500
GGGTTTCCA GTCTGAGGGT GAAGGATCAG GAGAGGGAGA CCTGACGGGT CGATGTGGGG 154560
CATCATCCAC TTGAGTGAGA ACCAGAGGGA TCCCGTCATT GCCCAGGGCA GATGCTCCAT 154620
TTTGGGGGGC ATCATTCACT CTTTCCTGTT CTCCCTGCAT TCCTCTGGCT CCTGCCAGG 154680
AGAGGTGGCC GCTGGCAAGA GAGCTTGTTG GAGGTGGGAG GTGGGAGGTG GGGGGTGGGG 154740
GGTGGGGAGT TCTTGAGCCA GGACCTAGCG CATAGTCTCC AGCCTGCTGA TGGCTGTCTT 154800
GGATGCTTCA AAGGGGAGAA GATCCTAGAT GTGGGAAACA TTGGTGGGCG TTCTGCTGGG 154860
GCATCTGTAG CCTCTGAGAA GGCTACCACT CTCTCCTAAG CTTACGCCGT CACACCCTGG 154920
GCACTTGTTG AATGACTTTA CTTAGCTTAC AGCCTCTGGT TCCTGTTGGG AAAGTTAGGG 154980
CTTGCCACAG TGTTCATTTT CCTTTGCGGG CAACTCCGTT CCTGGCACTT ATCATATTAC 155040
CCACTGTAAT CCCCCTTAG AGCTGTGTCA AGGTTCTGAG AATCTATCCC TTGGCTTGGA 155100
AGGGGTCATC TCTCTGGCCA GATCATTTCC TGATAGGTCC TGAGGCACCA CAACACATAG 155160
GAGGCTTGTG CTCTCTCTGG GGTTCACTGC CTGTCTCTT CTCCAGGTCA ATATGTGACC 155220
TTGGACCGGT TGCTTGAGTC CCCTGGTCAT TCAGAAACAA TTGGGTTTCC CTGGCTTTGG 155280
AGCCTGGCAG CCTGGCTTTG AGAACCAGGGC TTTAACTTGT CACATGACTA TGGCCAAGTT 155340
CCTGGGGCTC TCCAAGCTTC ACTTCCTCTG TAAAAAGGGC AATAATATAA TACCTGTCTT 155400
ATTGGGTTTT GTCCATGTTA GATGAGACAT TGGGTACAAA GCACTTGGTC CCGTGCCTGG 155460
CACATTTACT GCACTTAATG TATGATAGTT TTCTTATTAT TCTAATAAAC AATATGGCTT 155520
TGGGAGTATA GTTCTGCCAC ATTGCAGTGG CCAGAGTGAA GGTGGTGAGT GCCTTCTGGG 155580

FIG. 6.59

GCCCTGGGAG TCAAGGTTAT CCGCATGCCC TTTCTTGCTT GCTCCTCAGT GTGGCTGCCT 155640
CTATGTCCAC ACCATGCAGA TGCAACAGGT AGTTTGAACC TCTGAGGCCC ACAGTGGGAT 155700
GGGGAGGCAG GGACATCACT TATGGGGTGG GAAGTCACCC ATTCCCCAGG AAATGGCCCC 155760
AGCTGCCTTT TCCATGACTC CTCTTGAAAC CCTGTGGAGG CCACATTCGT GTTGGGGCGG 155820
TCTTTCCCAT GAGGATATGT TCAGATGCCG AGGCATTTTG AAAAGCCCTC CATAGAGTTT 155880
CCTTTCATAA CACATGATCA TCCCCTTGGG CTTCTGGTTT TTTTCTTTC AGGACCTTAT 155940
TTTCAGGCAA GTGGCCTTTG ACCTCTAAGG CTGTCCTTTC CTAGCTACCG AATCCAGCAT 156000
TCAAAGTGAT GGAAATATGT ATATATAGTA ATAGTAAAAT ATCAGCACTT AATGGCCTGA 156060
TAAGAATGTC ACTGCAATGC TGAGTTTGA CCAACATTTG CCTGCTCCTG CCATTGAGCC 156120
CGGGCTCCCC TCCAGAGCTG AGCTGCTGCA AGGGATCTGA GTAAGTAGGG CTGTGTCAGA 156180
GTGGCGATGA CAGCCACCAC ATGCTAAGGA AGAGATCCCC AAGGACAAGG AGAATCCCAC 156240
GTGGAGCTAC TTGCTTCTTT GTCAGTCTTG TTTTCTTAT TTCACAACCT TCTAAAACAC 156300
AATCTCTCAA CCTCTATTGT TAGCTTGCAT TTTTCAATCA TGAGCACAGC TTTACCTGGC 156360
TCCATGCTTT GATTGACTCT ACCTGCCAAC ACTGCAACAA CAGGGAAAGG GACACCGGCC 156420
TCATACCATT AGATGGTGTG TAGCCTGGGC ATGAGGATAA TTA AAAACTC CCAAGGGGAT 156480
TTTAACATGT AACACAGTTT GGAAACCATT GATGTAAGAT CTTCTTACTC AACATGTGCT 156540
CCAAGGAGCT GTTGTATCAG CTTATCAGAA ATGTAGATCA GGCCGCACTT GGACCTGTAG 156600
AATCAGAATC TGCATTTTAT CAGATTCCGA CATTATTTGT ATGAACATTA GCTTTTGAGA 156660
AGTGTGCTT TAAGAGACTA AGGGGGTCAA TCTACCTCAC TTTGCAGCTC TGTGTTCTT 156720
AGTCATTGGC TAAAATATCA GCCCCCTGC AATGAGCCAT CCTCCCTTGT ATAGTCAGTG 156780
ATGGCCTGTG AACCTTTAGC CAACTGGAAG TGGGAGGGGA CACAGTCCAC AAAACACTAT 156840
CCTGACTTTT GACACCAACT ACAAGTCAAG GGGTTCCCCA AACCACCCTG AGTTGTGATA 156900
ATTCGCTGGG AGATCTGACA GAACTCACTG AAGGTTGTTA TACTCATGGT TGTGATCTCT 156960
TATAGGGAGG GAATACAGAT TAAAATCAGC CAAAGGAAGA AGCACACAGC ACAGAGTCCA 157020
GGACAGTGCC TGACATGGAG CCCCTACGGT CCTCTCCCGT GGAGTCACGG ACAGCGCCAC 157080
TCTCCTGGCA TTGATGTGTG ACAACACACA GGGAGTGTTT CCCACCAGGG AAGCCTTGGT 157140
GTCCAGGGTC TTTACTGTGG CTCTGTCACA TGAGCACAGC TGAAGTCCCA TGCGGCCGAT 157200
CTGTTCCAG ACTCTCCACC GCTACACATC ACTCACAGTC CCTGCTCTAA ATCACACACC 157260
ATGACCCAAT GTCCCCGGGC AAATGAAAAC ACCTCTAGCA GGCAGGACGT TCCAAAGCCT 157320
TAGAGATCAC CTCTCAGAAG CTGAGGGCAG AAGCCAGACC TCTTTTGGG CAGGGTTAAA 157380
TTCTTTATTA CTGTTTTTGA AAAAATCCC AAATTGAGTT TTTCTCTTC ACTTACAGCA 157440
GCATAACAAC AATCATCAAT GCAGAAGACT TCTGCGAGCA AAGGTGTGGG GGAAAACCCC 157500
AAGCAGTGGA CACTAGCTGG TGTCTCCAA TTTGATTCTG ATGCTGTCTA CTGGGAGATA 157560
GTGTCAGATC CTCAAGCCTA AACCTCCTT CTCCCAGTCA GAGGGCTGGC CTTTGGAAT 157620
TCTGACCAAT CCACTTCAAG TTGAGGTTCC AACCCTCCG CTCTTGGGT TTGGTTGATT 157680
TGCTAGAGTG GCTCACAGAA CTCAGGGAAA CACAGCTACC AGTTTATTGC GAAGGACATT 157740
TTAAAGGATA AAAGTAGGCA GATAAAGAGA TGCATAGGGC GAGGTGTGGA AAGGTCCCTA 157800
GTGCAGGAGC TTCTGTCCAT GTGGAGCGGG GGTGCACCAC CCTCTCAGTA CATGAATGAG 157860
TTCTCCTTCA CCTGCCTATC AGCCTCTACA TGTTAGCTC CCAACCCAG TCCTCTTGGG 157920
TTTTTATGGA AGCTTCAAGA CACCCACATT CTTTCCCCAG AGTATAGGGC AAGACCTTCT 157980
CTGGGGAGGG TTTTAAGACC CACAGTCAGA AAGGTGGGGT GGGGTCAAGA TTAGAGTCCT 158040
GCCTTGACGG GCAGGTGAAA GGGGTAGGGG GAGTAGGTGA GAAAAATTCT GTTTATTTTT 158100
TCTTTTTTTT TTTGAGACGG AGTTTCACTC TTGTTGCCA GGGTGGAGTG CAATGGCACA 158160
ATCTCAGCTC ACTGCAACCT CCGCCTCCCA GGTTTAAGCG ATTCTCCTGC CTCAGCCTCC 158220

FIG. 6.60

CGAGTAGCTG GGATTACAGG CGTGTGCCAC CATGCCTGGC TAATTTTGT TTTTAATAG 158280
AGACAGGGTT TCTCCATGTT GGTCAAGGCTG GTCTCAAACCT CCTGACCTCA GGTGATCCAC 158340
TTGCCTCAGC CTCCCAAAGT GCTGGGATCA CAGGTGTGAG CCACTGCATC TGGCCAAAAG 158400
ATTCTGTTTT TGAGGCCTGC CTCTGAGGTC TAACACACTC AACATTATAA CAAGACTGTA 158460
GTAAGGGCTA TGGGAGTTAT GAGCCAGGAA CTGTGGATGA AAACCTATCA CAGATATGCA 158520
TATATATATA TATATATATA TATGCATATC TATAATAACT CCACAACCTAC ACACTGCCTT 158580
ATTGCTCAGT TCTTCTCTCC ATGTCTCTGA CCCACCCTTG CCCCCTTCCT CCATCCTTTT 158640
CTCCATTGCA TACCCATCCA CTGTGCCCTT TGAATGCTC ACACCATGAA CTGCAAACCTC 158700
TCGTGTGGCT TCAGCCTCTT CTCTGAAAGT TCCTCTCACC TATTACTTTC TCTGGAACCT 158760
GCCATCCCTG CCACCTTCTC AAAAAAGGCC TTTTATTCTC TTCATTCCAC AAAGCTCAGT 158820
GTCAAAACAT GGGGTTTACA CTGGAAGCTG AGGTCACATC AGTAGCCGGG ATCAGGGTCTG 158880
CCCTAGCTGC CCAATGCAGC TCCCAGGCCT CCTGTAAAAC CTTGACCTTT GAGGTCATGA 158940
CAGCCCTCTC CTGCTATGCT CATAGCTGAC CACTGAACTC CTGGACACTC CCTCCCCCAA 159000
GTTACACAGAG AATGTGGGCA CATGCCTTAC AGTCTCCCT TGATCCAAAC TACTGCCTTC 159060
ATCTTGAGTG ACAGCAGCAT CTTTGGATG TCTTGGCCTG TCTAGCTTTA TTTTTTGTG 159120
TTCTGCCATC AAGTTGCTAC TTCTGTTGCC ATCGTGCCTG TCAGCGCAGT GCAGGCTGTG 159180
GTGAAATCCC ACGAACTCAG GCATCACACT GACCGGGTCT GAGTCCTGTC TCAGTTGTCA 159240
GCTAGTTGTG CAATGAAGGG AAAGGGACCT AACTTTCCA AGCCTCAATT CACTCATCTA 159300
TGGCATGGTG ACAATAATGG AGGTTGATTT AAAGTCCTTT GTAAGAATTA AGAGTTATAA 159360
TAGACATAAA GTGCTGTATC TGGTATACCT AGAAAACATT CCATAAAAGT TAGTAATTGT 159420
TGGTCATGTA ATGATGACTC TCTAGGCTAG GATTTAGCT TCATTGCATG CACATGGTGC 159480
ACTCACAGGG CGTGACCTCT CTCTGTCTCA GTAACCTCAT CTGAGGACCG GGATAATCAT 159540
ACCGCTTCAA AGGGATGTCA TAAAGATTAA ATAATATGTG TAAGGCTGCT TGCATTTAGC 159600
TGCATTCAAC AAATATTCT GTATCTTCT CCTATTCT CTTACTTTC TTGCTTATTA 159660
TCTGCTCTAG GTATAGATTT CAGAGAACTA AGCTTGTTAC AATCCTTCAT AAAATAACCA 159720
GGTTGGTTAG GGCATTCCA AGAGTCAATA CTGTTAGTG ACTATTCTCT GTTTAATCTA 159780
TTTTGATTGT CCAGGGTCAT CTTTGTCTAT GTCATAGGTT GTTGGCTTCT TCTAGAGAAG 159840
TGAGACGATG GACAAGTTCC AAGTGAGTGA GCGACTGGT CAGGATATTC CGCTGAAAAA 159900
CTCATGTGAG TTCTAATTCG TGATTGTAAT TCAATCACAG CCTGAGAACA GTAGGACTGT 159960
AGTTCAAATG CTCTGTTCCC TTTTTTTTTT CCCAGAGGAT AATTTTTTTT TTTCTTTGAG 160020
ATGGAGTCTT GCTCTGTAC TAGGCTGGAG TGCAGTGGCG TGATCTCGGC TCACTGCAAC 160080
CTCCGCCTCC TGGGTTCAAG CAATTCTCCT GCCTCAGCCT CCAAGTAGC TGGGACTACA 160140
GGCACATGCC ACCACGCCCA GATAATTTTC GTATTTTATAG TAGAGACGGG GTTTCCCTT 160200
GTTGGCCAGG GTGGTCTTGA TCTCTTGACC TCATGATCCG CCCACCTCGG CCTCCCAAAG 160260
TGCTGGGATT ACAGGCGTGA GCCACGCGC CCGGCCTCTA GAGGATAATT TTAAATGTG 160320
CTTTTGCAAT TGGAAAATGT GATTGGCATT TTTTCTAAT TTTCTAATAT GATACGCTGT 160380
CGGATGCTAT GGATTACTTA AACCTCTGG CTACCTAGAA AGATCTTTAA GTGGTTCTCA 160440
ACAAGCTTCA TACGCAATGT AAATTGTATT ATCTCTCAGG ATGTGTGAGA ACATCTGTTT 160500
TTCTTCTAAT GCAGTAAACA TATAAGGGTC TCTTGGGATA TCTTTTAAAT AGACTTAATA 160560
CAACATTCAG GAATGATAAC AAAATATAAT CACAGTTGTA AGGGAATGTG AGCATTTTCA 160620
ATTAATAACA TTGGAACCTT ATGTTTAATA CAGTGTTAAA AGTTGACAAA CATGTAGGAG 160680
TCAGAAAATT CAATTAAAT TATCACAGTA ATATGAATTT AGCCACATCC TGTGTTAGTT 160740
ATGAAATCCA TTTAACACCA CAAACAGTAA TATTTTATAGC CAGTTTATTC AAAAGGAAAA 160800
CAGGAACTAA ACCACTTCA TGCAATATAT ACTCTGTAA TGTGGTCAGG CTAATTTTGC 160860

FIG. 6.61

TGGGGGAAGG AACTTAAC TTGAATATTT GAATGCCAG TCATTTAATC TGAATATCCT 160920
ATTTCTTGC ATGTTGCAAA ATTTTGTCA ATAAAAGGCA GAAAAAGAA TCTCTCTCC 160980
ATGCTCATCC CTAAGAGAAT GGGTTGTCTG TACCCTGAGA GCATTTTATG GAGGGGACAA 161040
CCACTTTTCT AATTTTCTT CCCACTTCTC TGTGGGCACA AATGCTCTT GGTTGAAAGA 161100
GTTGTAATTC AGTCCCAAGA TGAGGTGTGG TTAAGCATC CCTAACCTAT ATCTGGGGAC 161160
CCCACAGCCA CACACATGGG GGAAATGGAG CTTGTCATTC AGTTCTCCAG CCATTGCACA 161220
GGGTTTCATGG ACTCTTCGT GATCCACCCC CACGCTTCTT CTCTCTGCTA GCCGAACACA 161280
CTTCTCTCTT CTTTATCAGG AGGCCATAGG AGAAGGGCAT TCATTTTAA TACACATACA 161340
TCTGCATCAA GTCTAATTTT GCCATGTCTC AATCCAAC TGAAATGGGT TGTTTGGGGG 161400
CTATGGTGCT TATCAAACAT TTAAGCAAGA ATAGCCAAAA TTAGCCAAGC AAGGAGAAGT 161460
TCAGCAACGT TCCCAATGG CCCCACCAA GTACTGTAAG ACTGAGGATA GCTAAAGGT 161520
CTTGAGAGGG ACTTCTCAGG CAGTGGCCCC GACATTTATC TGTTTTTTA AGTGAGAAAT 161580
CTGAGTACCA TTCTTGACTC CTCTCCTTA CCCCCAACCC CTCCTAAGC CTTGTGCTAC 161640
TATTTAGTAA ACAGACCTC AATGCACAAA CTTCTGTCTA AGGCCATGGC CACCACCCTA 161700
GTCTAATCCA CCATCTCTT TCTGGAACAG ACCCCAGCTG CTCTCCCTGT CTCTGTGCTG 161760
GTCTCTCAAT CCATGCTCCA CACTGCAGCC AGAGTGCTCT ACAATGCAAA TCCATTTGTG 161820
AGACTCCTCC TCTTAAATC CTCAAGTGGC TTCTCTTGC CCCAGGATC ATTTTGAAC 161880
TCCTTAATGG AAGAGGCATG GCCCTTGGG ATGTGGTCC CCAACCCCTC CCACATCATC 161940
TTTTCAATCA GATTTCCAC TAAATGAAA TTTTTCAGG TCCTCAACTT TATGGTGACT 162000
TTCTCTTGCT CAGGATCTT GAACATACTG TTTCTCTT CTTTTGTAT TTGCAAGAC 162060
AACACTTCT CTGGTAAGAT TTTCTGACA TCCTCTATA AAAAGATTG AGATAGTTGA 162120
CTACCCAAA TGTTCCTT TCATTCCAAG CTCTATTCAA GGCAGTAAAG TGCCCGGCTG 162180
ACAGATTGCA TTCCTCATCT TTTCTGAAGC TAGCAATGGC CATGCAACAG CATTCTGGCC 162240
AATAAGATAG AAGTCGAAGT TGAAGGGTGG GATTTCCAAG AAAGCTCGTT GAAGACATAA 162300
TTCTCATTT CACTTCTTAC TCTTCTCT TCCTGCTTCC TAAATGCGG TGCAGATGGC 162360
AGACACTTCA AAGCTGTCTC AGGCAATCAG GTGATGTAA GGCAGAAACC AGCTTTATGA 162420
TGGGTAGAAC AGGAAGAAAG AAGGCACCTA TGTTCTTGT CACCTGAAC CACACCAGCA 162480
CTGCCTTGGC TACCCCTGGA ATTCCTTAA TGAGAGGCAA ATGAGAGCTT ACGTGTTTAA 162540
GCCATTGCTA TTTTATTTT TTTGTTTAT ATGCAAAAGA ACTTAATCCT AACTGATATT 162600
AACACTAAT GGGTCTATTG CTTGGTACCA AGCCAATGCA TGACACATGG TATATATGCT 162660
CAGTAAGTAT TTGTTGAATG AGTGAGGCAA TGAAAGAACA TAGAGGATAT ATATAACAGT 162720
CCTCTGCCC AGATGTCATC TGATCCTCT TAGGATCTGG GCCATAAAA CTGTATCTGA 162780
TATAGTTTGA ATATTTGTT CCTACAAATC TCATGTTGAC ATTTTATCCC TAATATTGGA 162840
GGCAGGGCCT AGTAGGAGT GTTTTGGTCA TAGTGATAAA TGGCTTGGT CCGTTCTCAC 162900
AGTAACGAGT GAGTTTTTAT TCTAGTGGT CTGCAAGAA CTGATTGTTA AAAGAGCTTG 162960
GATCCTTCCA CCCCTCTCTC ACTCTTGCTT CCTCTCTCTC ACCTTGTAAT CTCTACAAGC 163020
TCTTCACCTC CCCTTCTCT TTTGCCATAA GTGGAAGATT TCTGAGGCCT CACCAGAAGC 163080
AGATGTTGGT TCCATGCTT TGTACAGCC TGCAGAACCA TGAGCCAAAT CAACTTCTT 163140
TCTTTATAAT TATCCAGTCT CAGGTATTCC TTTATAGCAA CACAAATGGA CTAAGACAGT 163200
TTCTAATGCT ATGGTCTT TAGTAGGTCA GTGTAAACC CTGGATCACT CCTGTAACAA 163260
ATTACTTGA ACTCTTCTCA CCATACATAT TAAAAATAG TTGCCATGTT GAAAATCCTA 163320
TAAGATCATA TTTTATTCA AATCCAACAA CTCATTGCTA AGGAGATACA AGAAGCAGAA 163380
AATACAGAGA GACTAATGTG TTGATGATT TTGTGAGGGA CATAAGGTCT GTGTCTAGAT 163440
TCATTTTTT GCATGTGGAT GTCCAGTTGT TCCAGCACCA TTTGTTGAAA AGACTATCTT 163500

FIG. 6.62

TGCTCCACTG TATTGCTTTT TCTCCTTTGT CATAGATATC TGGTCACCTT ACCTTAGAGT 163560
CACAGATGAA TGGTCCTATT ACTTAACTAC TGAAAATACA GGCCAAAGCA AACAGAGGAA 163620
TAAGGGATAT ATAATAAGT ATTTGTGTAC TTGACTTGGC TCTAAAGGAA GCATTGCGTG 163680
TCTGTGTAAG AAGAATGGGT GAGAGTTTTT CACCATTCAA TATTTCTAAT CTTTCTGAAA 163740
TACAAAGCCA GGACATCCTC TAATCCATAC ATTCCATAGT TTGGTTAATA TAAATTCCTT 163800
TATTAAATCC TTATTAAATA AAGTTATTTA TGTTTCTATG AAACCTCATTT TAACTCCTAA 163860
GTGAAAAATA CTAAGGAGCT AACTAAACAT CAAACATTTT TAATTTTTTA AATTTTTTTA 163920
GAGACAGGGT CTTGCTATGT TGCCCAGGCT GGCTTTGAAC TCCTGTGCTC AAGCGATCCT 163980
CCAACTCAG CCTCCCGAGT AGCTGGGACT ACAGGTGCAT GCCACTGTGC TCAGCTAAAC 164040
ATTTTTTTGA AATGCTCTTT TAAAATCAAT TTTATTGAAG TATAAGTTAC ATACCATAAA 164100
AGTACTCATT TTGAGTGTAC AGATTGACAA GTTCTGACAA ATGTGAACAA CCATGTAACC 164160
ATCACCAAAA ATAAAGATAT GAGACATTTT CATTACCCCA AAAAGTTCCC GTGTCCCTCT 164220
CCAGTCAATA TCCAGCCCTA GCCCCAGCTC CAGGCAACCA CCAATCTGCT TTCTGTTGCT 164280
ATAAATTGTA CTTATCTTTT CTAGTGTTT ATACAAATGG AATCATACAG CATTTACTCT 164340
TTTGTGTCTG TCTTCTTCTG CTCAGTGTA TGTTTTGGAG ATTCATCTAT GTTCTGTGCC 164400
TCAGTAGTTT GTTCTTTTTA TTAAGGATA ATTCCATTAT AAGAATATAC CACAATTTGT 164460
TTATCCATTT ACTGCCTGAT GGGCATTGGT TTGTTTCCAG CTTTGAACCTA TTTTGAATCC 164520
TAAAAGACTG CCAGTTTTGA ATGAGACCCC AGAACAATGA ATGTAGGCTC TGTATACAAG 164580
TTCAGGCTGC TGGGCAACTT AGGCCTTAAG ACACAACCTC GCCACTTAGG CCTTAAGACA 164640
CAACTGACAT GATGGTGCTT AAAGTGGCTG TGATGGAAAA GGAGGCTGTT TGGAGCCTTT 164700
GGAGTGCCTT TATAGGTGAA CCCCAGCATA GCACCTAATG ATTTGGAGCA AAGCTGTGTC 164760
ATTCCCCAAA GATAACTATT CGCCTTTTGA GAAACATCTT CTAGCTACTA TCAATAATAA 164820
ACACAGAATG CATCACCATG GGCCACCGTG TTGTCTTTTG ACCTGAGTTT CCATTGTGAA 164880
CAAGAGTCAT TTGATCCAAG GCAGAAAGTT GGGTGCACAC AGCAGTGTTT CATCATCAAA 164940
TGGAATATGA GATTGGGCCC AAGTAGGTCC TGCAGACACA AATAAGTTGC AAGAGCAAGT 165000
AGTACAGGCG CTTGGCCTGG CCAGTACTGT TGCCAAGTTG ACTGCTTCCC CTCAGTCTGC 165060
ATCTGTGGCT TCATGGGGAG TTTCTATGA CCACTTGATG GAGGAAAAAA CAAATTGGAG 165120
CATAGTTTAT AGTGCTGGTA CTACCCAAAG TGGCTAGCTG AGGCACTACA TCTCCACTCT 165180
GGGGTGCCCC TGAAGGACAG TGCCAAAGGA AAACCCCTC AGTGAGCAGA ACTTGGAGCA 165240
ATACAAGTGG GTGTTTATTT TACCTAGAAG AGAAGATGTC CGTGAGTTAC AGATCTACAC 165300
AAAATCACAG AGAGTGGTTA ATCGTTTGTG CTGATGGTCA GGGACTTCCA AGAGACATGA 165360
TTAGAAAACCT GGTGACAAGG AGTCCTGGGG AAGAGGCATA TGGATACCTC TGAACACACA 165420
CAAAACATGA GAATATGTAT CCCATATGAA TGTTAACCAA AGAGCAGCCA CAACAGAAGA 165480
GGATTTTAAA ATCAGCTGAA TAAGATGATT CATTCTGACA GCATCAGCTA GTCTCTTTCC 165540
CCAGCCACTG TTGCCAGTG GGCTTACATA TATCATGGCC ATGGGGGCAG GGCTATGTAT 165600
GGACACAGCA ACATGAATTT CCACTCATCA AGGCCAATTT GGCTCCAGCC ATTGCTGAGT 165660
GCTCAGCCTG CCAAGATAGA AATCTACGCC AATATGGCAC CATTCCCTGG GCTAGAAAAC 165720
CAACTGGTGG AAGGTTGATT ACATTGGACC ATTTCCATCA TGGAAGGGGC AGTGCTTTGT 165780
CTTCCCTGGA ATAGACATTT ACTCTGGATA TGGATGTGCC TTCCCTGACT ACTACAATGC 165840
TCTGCCAAAC CTACCATCCA TGGGCTTAAT TTTATTTGTT ATAAAAATTC AACCACCATT 165900
GCTTCTGACC AAGGAAGTAA TCTTACAGCA AAGGAAGTAC AGATATGAGC TTCTGATCAT 165960
GGGCTTCACT GGCCTCACAG TGAAGCAGGT GGCCAGATTA GAACAGTGGA ATGGATTTTA 166020
AAGGCTCAGT TACAGCACCA GCTGGGTAGC AACACCCTGC TGGCCTGGGG TTATGTCCTG 166080
CAGGATGCTT TAAGTCAGTG ACCAATATAT GATGCTATTT CTCCCATTTG CAGGATTCAT 166140

FIG. 6.63

GGGTCCAAGA ATCATGGGGT CAAAATGGGA GTGGCTTTTC TCACTATCAC CCTGGTGTTT 166200
GGGTAGTAAT TTTTCCTTCC CATTCTGTGA ACTTTGGGCT CTGCTATTGC AGAAATCTTA 166260
GCTCCTGTGG GGGGAATGCT TCCATCAGGG AATACAATGG TGGTTCCACT AAACCTGACAG 166320
CTGAGTTTGC CATCTCCTCG TGCCAGTGAA TACACAAGCA AGGAAGGGGG TTCCTTTCTC 166380
ACCTAGGGTG ACTGATCCTA ATTACCAAGG AGAAATTGGA CTGCCACTTC ACAATGAGGG 166440
TGAGGAGTAT GACTCTATG TGTCTGTGAT TAATGTCAAT AGAAAGTGAC ACCAACCTAG 166500
TACACAGAGG ACTGATCATG GTCCAGGCCC TTCAGGAATG AAGATTTGAG TCACCAGGCA 166560
AGGAACTTGG ACTCACTGAG GAGGGCATAT TCCAAGGAGA ATATTTTATC TATGTCCATC 166620
TATGTCCATC TATATTCCAT CTGTGTTCCC CTTGGAATTC CTATTCATGA ACATGGGGAA 166680
TTCCAAGGGG AATATAGAAT GAGTAGTGGA AGGTAGTTAT AAATGTAAGT CAAAAACCAC 166740
ACAACCAATT TGAGAAATGA GGAAGGTAAT AGTGTTGAAT ATGTCTTCTT TATCTTGATA 166800
TAAATGTATT TGTGCATATA TTAACCAGTT TATTTATTTA TTATTATTTT TTGAGATGAG 166860
CTCTCGCCAT GTTGCCCAGG CTGGTCTTGA ACTCCTGGGC TCAACTGATT CTACCATTTA 166920
GTCCTCCGAG TAGCTGGGAC TACAGGCATG CACCACCATA CCCAGCTGAC CAGTTTTTTC 166980
CTATTCCTCT ACTTAATTC TCTACTATAC AACATAATAT GTGTTAATGG TAGTTAACTT 167040
TATATCTCAG TATTAAGTCA CAAGATATCA AAAAGGGGAAT GCGACTTAGT TACAAGCAGA 167100
ATGAATATCA CTCAAAGATG AATAAAGAGA AGAGGGTTAG TGCATTTTCT GTTGATGAG 167160
AGAAAGTTTC ATTGTTAGGC AGAAGCATGA TTTTGCCTTT TTTTTTTTTT TCCAAGGTCT 167220
CACTCTGTGG CCCAGGCTGC AGTGCACTGG TGCGATCTTG GCTCACTACA ACCTCTGCCT 167280
CCCGGGTTCA AGTGATTCTC CAGCCTCAGC CTCCAGAGTA GCTGGGATTA TAGGTGCGCC 167340
AGGTTAATTT TTGTATTTT AGTAGAGAAG GTGTTTCTCC ATGTTGGCCA GGCTGGTCTT 167400
GAACTCCTGG CCTCAAGTGA CCCACCTGCT TTGACCTCCC AAAGTGCTAG GATTACAGGT 167460
GTGAGCCACT GTGCACAGTC ACCACGGTCT TTTGGGAGG CAACTTTAGC ATGGTTAAGA 167520
GGTGCGAATG GATGTTAAGC TAACACCAGG TAAGCCCTGG TAGATGTGTA TTGTGTCAGT 167580
GGGCCTACGC TGGAGCCATG TTTCCCCAAA TTCACTTTTC CTATGTACCT CTGGATTAGT 167640
GTGGGCCACT GGAGACATTT CACATGAGAT GAGGAAGGTG GGAGTGAAGG AGCAGCATCT 167700
TTTTACACTA AGCAGGTCGG GGAGGGCATG TGGCTCTGTC TCACATTGTT GGGAATCTGT 167760
CCATCATCTG GTTGGCTTAG GTCAGTGGGT GAGTTCACAG CTGTTCCAGC TTCTGCTGGA 167820
AACTCCTTCG GTTTCTCTGA CTGCTCCGTG ATGAGGGCAT CAGATTCTCC TGCAGAAAGC 167880
CCCAGTGTTG AAGTTGGGGC TTCATGTTGG TGAGTGATAG TTACGGGTTT TAGCCCAACC 167940
TGTGGTTTCT TGCAATTTT AGTGTCAGCT CAGTCTTGCG GGTTTGGGT TGTCTTGCT 168000
TCCCACACTT CATGCCCTTC TTTCCCTCCT GACAGTCTGC CCTTTAGATT TTAGGATTCA 168060
GCACCAGCCA CAGAAACAGC AACCTCACTG TTAAGGGTTG AATTGTATCT CCCCCAAAGG 168120
TAGGTTGAGG CCCTACCTGC CAGGACTTCA GAATGTAACC TCATCTGGA ATAGCATCAT 168180
TGCAAAATA ATTAATTAAG ATGAGGGCAT ACTGGCTCAG GATGGGCTCC TAATTCAATA 168240
CAACTAATGT CCTTCTATGA CAGCCACAGG AAGACAGAAA CGCCAAGGGA GAACACCATA 168300
TGCTGATGGA GGCAGTGGA GCTGCCAGCC AAGGATTATA ACCAGAAGTC AGGAAAAAGC 168360
AAGAAGGAAT CCTCCCTTAG TGATTTTACA GGGAGCATAG CCCTGCTGAC ACCTTGATTT 168420
TGGACTTTTA TTCCCCAAAA CTGTAAAAA ATACACTTCT GTTGTTTTAA GCCACTCAGT 168480
TTGTGCTACT TTGTTATGGC AACTCCAGAA AACAAAAATA CACTCAGACT GTTTAATCAA 168540
CCTCCATAAT TGCATAAGGT CTAATCCCTA TAATAAATCC CTAAAAATG TCTGTGTATA 168600
TATATTTAAA AATATAAAAT ATCTTCTAGT GGTCTGTCAT CTCTGGTCAA TCCCTGACTG 168660
ATACAGAATA TGTATTTTCA TTTCTAATGA TGAAATACCT GAATGAAAT TCTAGGACAT 168720
ATGGTAAGTG TATGTTTAGC TTTTAAGAAA CTGCCAACTT GGGGGAATTG CTTGAGGCCA 168780

FIG. 6.64

GGAGTTCAAA CAGCCTGGGT AACAGTGATA CCCTGTCTGT ACAAATAAA AAATATTAGC 168840
AGCGTGTGGT GGTGTGTGTC TGTAAGTCCCA GCTACTCAGG AGGCTGAGGT GGGAGATTCA 168900
CCTGAGCCCA GATCTTTGAA GTTATAGTGA GCTATGATCA CGCCACTGCA CTCTAGCCTG 168960
GGTGACAGAG TGAGAAAGCT GGTCTCTAAA AAACAAACAA ACAAAAAAGA AACTGTCAAA 169020
CTCTTCCCAA CATGTTGCCA TTTTACATT TACCATTTTA CATTCTTACC AGCAATGATT 169080
GATAGTTCCA GTTGCTCCAT ACCCTTGCTG ACCATTCCAA TAGATGTATT GTGTTATCTC 169140
ATTGTAGTTC TAATTTGTAT TTCCCTAGTG ATTAATGATG TTAAACATCT TTTTCATGCAC 169200
CTATTGGCTA TATGTATATC TTCTTTAGCA AAATATATGT TGTTATTGA AGAGCGGAAG 169260
TTTTACATTT TGATGAAGTC TAATTTATTG ATTTTTTTTT TCTTAGATGG CTCATGCTTT 169320
TTGTGTTATC TAAAAAAAT TTGCCTTCTT CATGGTCACA AAGACTTTCT CCTATGTTTT 169380
CTTTTGAAG CTTTATATTT TTAGTTTTTA TGTTATGTT TAAGACCCAT TTCTAGTTAC 169440
AATTTGTGTG ATTTTTTGA AGGGTCAAGG TTCATTTCT TTTCCATAAG AATGTACAGT 169500
TGTTCTAGCA CCCTTGTTAA AAAGACTTTC CTTTCCCCAT TGAAGTACTT TGTCAAAAAT 169560
CAACTGAGCA TATATGGGCA TCATGAATTT TAATCCTGTT AGAAGTGAAT GTTCCCAAGG 169620
CAGGCCATGC CCATGACTGA CCTCCTTTCC TTGGATTGCC TACAAAACAG ATAAAGCTAA 169680
GTCTGGAGCA AAGAAATCCA TGTCTAACCT GTATTTTTTT TTTTTTTTTT TTAGATGGGG 169740
TCTCGCTCTG TCACCCAGGC TGGAGTGCAG TGGCGTGATC CCAGCTCACT GCAATCTCTG 169800
CCTCCTGGGT TCAAGTGATT CTCCTGCCTC AGCCTCCCGA GGGGCTGGGA TTGTAGGCGT 169860
GCACCACTAT GCCCATCTAA TTTTGTATT TTTAGTAGAG ATAGGGTTTT GCCATTTTGG 169920
CCAGACTGTC TTGAACCTC GACCTCAGGT GATCTGCCTG CCTCGGCCTC CCACAGTTTT 169980
GTGATTATAG GCATGAGCCA CCGTGCCCGG CCTTAACCTT TGTTTTCTTA CACAACACAC 170040
TACGTGATGT TTTCCACATG CATGGGTCAT TTGCTTCATT TACGTACAAA TGCATAAGCA 170100
ATATACTGTG TGGTGTGAGT TTGTGATGGG AAAAGGAAGA AGTTTTGCGG ATACTACACT 170160
GGCTTCCTGC TATCTGTCTG TGTGAATGGC TATGGACTTT GTCTTCTATT TGTTGCTTA 170220
GCGCAGATAT GATCAGCTTA CAACTTAAGA TTCTAGAGAA AGAGGGTCAT ATCTGTAAAG 170280
CACTCTGAGC ATGTGTGAAG TTTAATCAAT AGCATATGAG GTTACAGCAA ATTCACTATC 170340
TTTGTCTCT CAGCTATAGA ATGGCATGAG GATTCATCTC AATTTAGTTC AATTCTGTTC 170400
AGAACCATGA GCTAGCTGTT CATGGAAGGA AAGCCCACCT GATTGTGGCC AGGGAAGGAG 170460
AAACAACACT TTAACCAGGT TGATTTGGTT CTCACAGACA CCATTGGCAT GTGACATCTG 170520
GAACAGACCA TGCCTGGTCT CTGTTCTGAT CACTTACTAT TCAGCTCAAT ATTGGTCTGA 170580
ATATTCTTTA GACTGACTGA AATGAAAAGG AACTGTTGTG TAACCATCCA TAATTCCAGC 170640
CTGTAGACCT GGGCTGTATC TCTATGCCCT GCCTGGCACA GACCCACCT CCTGCTCCTT 170700
CTCCCTCACC ACCAGTCAAT CCTTGTCTTA ATGAACAGGG AGGGCAACCC TGAATGGGGA 170760
GTGGAGGGAA GAGATGTCAT GAGATGGCAA CGTGACCCT GAAGTGAGGA TGAAGGCTAT 170820
GTGAATGTTG TAGGCTGACA GCCGGGCATA GTGGCCCCGT TGCCATGGCG ATGGAGGCAT 170880
GTTGATGCGA AGTGTCTGCA CAGCTCCTAG GATTTTAAAC AGCAGCTGGG CAGAGCCTCG 170940
GCGTCCCTGA ATTGTTGCCC CCCTGAGTCA CTGCTTGGCC CCAGCTGTCC TGATCTCTGT 171000
TGACAAATGG TTGTCCTTCA CAGTCAAACCT ACTAACAGTA CTCTAATTAA TGAATGTGCT 171060
AATTATTCTT GCCTACTCCC AGCATATTTG TCTAACTAAC CTGTCACACA CAGATCAGTG 171120
CAGCATATGC ATAATTACGG AGAGCGCTGG GAGCAGGGGA TGGGTGGGAG AGGGGTGGGC 171180
TCGCAGCCCT GTCGCTGTGG GATATTTCTT GTAAAGTTAC CTTTGCTAAC GGTGAGATGT 171240
CGTGGGGATA TGTTATTTCC CGTGAAGTGT ATATGTCTTC CTTTCTTTCC TTTCTAAGAA 171300
TCTCTCTTCA GGGCTGAGGG GCCATTGCTC AGTGCTTTAG CCTGTGAGGG GATTGCCAGG 171360
TACAAATGCA GAAGGACCAG GGAGCCCAGG TTCTGAAGAC GATTCCGGTA GCAGCACGTA 171420

FIG. 6.65

GGGTGATTAA AACTCCAGAC TTAAAGCCA GACCGGCCTG GGCTTGAACC CTTGTTCTGC 171480
TCCTTGCTAT GTGGGTCTTT GCCTTGACCA CATTTTTTTT TTTTTTTTAA GACAGGATCT 171540
CCCTCTCTTG CCCAGGCTGT AATGCAGTGT TGCATCACA GCTCACTGAA GCCTCCATCT 171600
CTACAGCCTC AAGCGATCCT CCTGCCTCAG CCCCAGTAG CTGGGACTAC AGGTCTGTGC 171660
CACCACGTCC AGCTAATTTA CTTTGTAGA GTTGGGGGTC TTGCTATGTT GCCCAGGCTG 171720
TTCTCCAACCT CCTGGACTCA AGCCATCCTC TAGCCTCGGC CTTCCAAAGT GCTGGGACTA 171780
TAGGCGTGAG CCACGGTGCC AGGCCCTTGA CCACATTTTT AACCCCTCTG AACCTCAGTT 171840
TCACTTTCTG GGCAATGGGA GGGGGGTAAT TTGTCCCTCA GAGGGTTGCA CTGAGGGGCA 171900
AATGTGAGGC TCTGGGTACA ATGCCAGTA CAGACTAGGT CCCCACGACA CAGCCGCTCA 171960
GCGGCTCCGG ATTCTGGGCT GCTCTGGA CTGCGCCAGGC GGTCTTCTGC GGAATCCGG 172020
GCAGGCAGGG CGGGCTGCGC TCCCCTCCCC GGCTCTCCCG GTGCCCTTG TCTTTTGT 172080
CTGTCTCAGC AGCTCTCTAT TAAGATGAAT GGCATTTCCA AAGGCTTCAC CTCTGATAAG 172140
TGTTCTCTG CAGCTGCAGC CAGAATCTTA ATGTGCGCGC TGAATTTAA TGGCCGTCTC 172200
GGCTATTAAC ACGCTCTTCT CGGGTGAAGT GGA CTCCCTC CATCCCCGGG CCTCTGCACG 172260
TGCTCTGCGC GCTGGCTGGG GGTGACTCCA AGGAGCTCAG AGCGGGGTGC CCGGCACCTC 172320
TCGCCAGGCG CTTTCGACC TTCTAAAGCG CGAATGGCTG GACTTTTCTC CCATGTGTGG 172380
GGCCCCAGAA GGTGTGGGGC CCCAGAAGGT GTGGGGTCCC TGCGTTCCAC GGAGCCCGGA 172440
AGGTTTCCAG TGATGGTGGG GGCTGACCAC GTTGGTCCCC GTGGGTGCTG TTTTCATGTG 172500
CCGGCAGATT GGGATGAGTT TAAAAGACAG AAGCGTGTAG GATAGAGAAA CTTCTTTAAA 172560
AACTGGAAAT TTTAATCTGG GGATTATAAC TATTGGACAG TCAAGTGCAA GAGTGAATAC 172620
ACTTCTCACT CCTCCTCCC AATTTTTATT TGCGGGATTA GTCAGTCCCC CTCTGCCACA 172680
TGATAATTGT GAGAACTACC AGGGTCTTCA TTCTCCTGCC ATCTGGTTGA CCTCTCCAAG 172740
AATGGACACC CGGGCAGCCT GGGCCAATGA GGCTGTCTA AGAGTTTAGA TGAGAGAAGT 172800
CAGTCTTTGA CAGGTGATGG AAGCTGTAAA ATGTAAAAC CCACAGTTGG TGAAGATGTC 172860
TCCAGGAAAC AGGTCTGCAG AGAGAATACG TTTGACATGC TAAGAGAAGC TGAGAGAGAG 172920
CGAGAGGAGA GATTGGAAGA AAGACAGAGA CAGAGGTAGA GAGAAGGGAA AGAGAGAGAG 172980
AAAGGGACAG AAGAGAGAGA AAAAGAGGG GGCCGGGCGC GGTGGCTCAC GCCTGTAATC 173040
TCAGCACTTT GGGAGGCCGA GGCGGGCAGA TCACGAGGTC AGGAGATCGA GACCATCCCG 173100
GCTAACACGG TGAAACCCCC GTCTCTACTA AAAAATATAA AAAAAATTAG CCAGGCGTGG 173160
TGGTGGGTGC CTGTAGTCCC AGCTACTGAG GAGGCTGAGA CAGGAGAATG GCGTGAACCC 173220
GGGAGGCAGA GCTTGCACTG AGCTGAGATC GCGCCACTGC ACTCCAGCCT GGGCAACAGA 173280
GCAAGACTCC GTCTCAAAA AAAAAAAAAA AAAGAGAGGA AGGGCGGGAG AGAGAGAGAG 173340
AGAAAGCTCT CTAGCTCCAA GGCCTAACCA CATCTCTGTT CTTTCAACT TCAGCTGTCA 173400
GATTTTGA CTCTTGAGT GAATAAATC TCCTTTTGC TTAACTAGT TTGAGCTAAG 173460
TTTCTATTGC TTGCACTGG AATACTTGT AAGAGGACTG GCCTTCATT CTGATGCATT 173520
GTCACTAAGA TGTAAGTGT AGAAGAGCTA ACGCTTTATG GGGTTCAAAC TCCTTGCTA 173580
CCAAAACCTA AACATCCCC GAACTTACC AAAGTGCAGG TATGAATTGG ATCTCACTAA 173640
GGTGAATATA CAAATCTTGC AAGTGTCTGAG CCCTAACCA TCTTGTAATA ACTCTGTGGT 173700
AGTTAATTT ATGTCAAAT GATTGAGCTA AAAAATGCC AGGTAGCTGG TAAATGTTT 173760
TTTTCTGGGT GTGTTAGGGA GGGTGTCTT GAAAGAGATC AGCACTGGAA TCAGCGGACT 173820
AAGTAAAGAA TTCCACCCCT CACCAATATG GTGGGTGTCA TCAATCCACT GAGGGCCTGA 173880
ATAGAACAAA AAGCGGGCAG AAGGGCAAAT TCCCTCTTCT TCTTGAGCTG GGCCATCCAT 173940
CTTCTCCTGC CTTGGACAC TGGAGCCCC TGTCTCCAG CTTTGGATT CAGACTGGGT 174000
CTTGACCAT TGCCCTCCAT CTTCTCCTGC CTTGGACAC TGGAGCCCCT TGTCTCCAG 174060

FIG. 6.66

CTTTTGGATT CAGACTGGGT CTTGCACCAT TGCCCTCCTT GATGCTCAGG CCTTTGAATG 174120
CAGACTGGTC TCCACCAGCA GCTTTTCTGA GTCTCCAGCT TGCAGATGGC AAACCATGAA 174180
ACTTCATGGT GTCCATGAGC ATGTGAACCA ATTTCTATTA TAAATCTGCA ATATATATAT 174240
ATGAGGAGAC TTATTTATAT ATTGGTTCAG TTTCTCTGGA GAGCCTTGGC TAATATAAAG 174300
TCTATACTCT ACAAAGTGCC CTAGGTACTC AGGGAGTACC CAAGTGTGTC ATGACCAGCC 174360
CGACAGCCCT GGCTGCTGGC TTCCCCGCAC ACAACTCTGC ACGCTGCCTT CATCAGCCTT 174420
TCTCTCTCAG CTGAACCGAG GGCATTGAAG CGGGCCTCTG GCACTGTACC TATGAGGGAG 174480
CAATATCTTC CCCTACACTG ACCTCTTCCG TGCCGAGATG CAGCCCTCCC TGCTGCCACT 174540
AGTTACAGTG GTCCATGTTT CCTTTCAAAG TGAAGTTTTG ATAAAAGCAC CTCTTAACCA 174600
ATGCCAAATA GCTAAGTCTG GGACAAAGAT TGCAGGTATT TTGCATTTTC CATGTAACCT 174660
CAGAGGGATT GCCATTACA CTGATCTGAG CTGCAGAATA CCAGGCAGCC ACCTCACCCA 174720
CCCAGCAGGT CCACTCTTAT ACTTTCTCAG AAAGCACAGC CACTCTACTC TTATTCAGTT 174780
GAAAAGAATT TCCAGGAAGG TGTTTCTGCG ATTGCCTCAG AAAAGTCAGT TCCCTTTGGG 174840
AATTTCCCTT AGGGATCATC TGTAACCCA TTTCTGCCCT TTACCTGAAT TCTTTGGTTT 174900
GGTTTGAATT CTTTGGTTTA ATTTATGAAT TCCCTTTATT ACTTTTCTCT GAAGAAATGG 174960
AGATATCAGC TGCCCTCCC CACTGCCATT TATTCCTTCC TTCATTCAA CCTTATGTGG 175020
CTGCTACTTA CCGTGTGTTA AGTGTTCACT TTTTCTTGG GAATCAAAA AAAGAAGGAC 175080
AGTATTTGGG GCACAGATCT TTTGGTGTTT TATACATTTT TTTAAAGTTT CATTTTACAT 175140
TTGTGTGTGC GTGTGTGTGT GTGTGTGAGA CAGTCTTGCT CTGTTGCCCA GGCTGGAGTG 175200
CAGTGGCATA ATCATTGGCT CACTGTAGCC TCAAAGTCCT GGGCCCAAGC AATCTTCCCA 175260
CCTCAGCCAC CCAAATGCT GGGGTTACAG GTTTATGCCA CTCTGTCTGA CCTGAAAGTT 175320
TTGGGTTTAC TTTCCCTTCT TTCTCTTTCG TGAAGTCAGA GATGATGGCA GCTTCCAGAT 175380
TCTCTGGTGC CTGTGCTGGG CTCGTGCTGG TCATGGTCTT GGGTCCAGGA TTCATTCTGG 175440
AGACTCTCAG GGAAGTTTCC CATGACAAGG AAATGTAGGA GAGTGTGCTG GCTTTGCGTG 175500
CTCCTCTGCC AAGCCCTGCT TCTCCTGGTG GGACACACTG AACCACAGCC AGGGCATTTT 175560
GGTGGTTAGT TAAAAAAAAA AAAAAAAAAA AAAAAAGGAA GAAGAAGGCA CTGTGTAATT 175620
GTGCCGGGGA TCTTCAGAAA TTGTAATGAT GAAAGAGTGC AAGCTCTCAC TTCCCTTCC 175680
TGTACAGGGC AGGTTGTGCA GCTGGAGGCA GAGCAGTCCT CTCTGGGGAG CCTGAAGCAA 175740
ACATGGATCA AGAACTGTA GGCAATGTTG TCCTGTTGGC CATCGTCACC CTCATCAGCG 175800
TGGTCCAGAA TGGTAAGGAA AGCCCTTCAC TCAGGGAAGA ACAGAAGGGG AGATTTTCTT 175860
TGATGGTTGT TTGGAAGTCA GGCTTAAACA ATTGTGTCTG TGTGTGCGCA TGCACAAACA 175920
CTTTTACCTT ATCTTTATTT TCTTCTTTT ATTGAATGT ATAGGGTTGT GTGTATTTCT 175980
GTGTAAATTT GGGGTTTTTC TCCTCTTAGT CTTTCACTTT TGTGGTGATT ACCAGTCCCA 176040
TTTTTAGAGC CAGGGCTGCA ACTTGAAGGT TTTGCTAAAA CCCTCACCGA AGTGTCTATG 176100
ATCAGCATTT TAACTATTAA TTAATGTGGC CAGGCAAGGG GTGGAAGGTG AGAAGACTAG 176160
AAAGGGAACA TGATATACAC ATTTACTCAG ATACTGGGCT TTTCTAACAT CTGCAGTGCA 176220
ATTGAAGTTA CCAGTCATCT GCAGTCTAAA AAGAAAGTGA TTTTGGGAGG TGCGTAGAAA 176280
AAATCATCTT ATTATTTTTC CTCTATATTA CTTTTTCTT TTTTCTCCT GAAGAACTT 176340
TTTTTTTTGG TGATACCTC TTTTCTCTA GCACGTATAA TTTTGAAGC ATTTTTCATA 176400
TGCAGTGTAT ACTTCAGAAA GAGAGAGAGA GAGAGGAAAA TTGTCCTGTT CAGCGTTTGC 176460
ATTTCCATTA TTCCTGCTAT TAGTTAAAA CAACAACAAC AACAAAAAAC AAGCAGGATA 176520
CCTAGATCTG GAAAAGGGAG AATTGTGTAG AGCTGTCTTC CTAAAGTTCT GAGTTAGGGC 176580
TGCCTCAGAC CACTTTCATA ACTATCTCCA GTGGCTTTGT GTTTTATATT TATTAAGATA 176640
GAGAAAAAAA GAGTAATTAC TAAGGGCAGC TGCTGTAGCT TTATGGTGAT TACTGAACAT 176700

FIG. 6.67

TGACATGCTG TCACGTTTTT GGAACCTTGA GTATTTAATC ACTTTGGGAT ATTCTATTTT 176760
CCCCCATCTT GAGTGTGGAC AGATGCTGGT GATGTAGCCT TCTGGGCACA GAGCAAGCCT 176820
CCCCCTCAGC CTCTGCACCA GAAAGGCTCA GCTTCACACA CTCCAAGTAT GTTTTCTACA 176880
AGAACTACAC TTTGTGGCTT TCTGACCCAA ACATTTTTAT ACTAAATTAC ACACAACAAA 176940
GTTGTAGCTC AGAGAGGGAA CAAATGGCTT ATTTAGGCCA CCATTTTCTT GAGCCATTAT 177000
GATTTACACAG AGGGCTCCCT TGGCCCTGTA AATTGGCAAG GATTCCATTA TTCAACCCGC 177060
ATACATGTAC AGAGACCCTG CTCTGGCCCA GATAGTATTC TGGGTACAGG CGGATAGAGC 177120
AGGAAACAAA ACAGCTACAG TGATGGACAG GTCAGCCTGC AGCAATGCCT GCAGTCTCTG 177180
CAAAGGTAGC TGTATGGGTG GGCAGGTGGC TAGCACTTAT TCAGCTCTGG AAGGATCTCC 177240
CCTCTGGCCT CTCCCCTGAC ACCCATCAAT AAAACTGAGG AGCATCGGTG GACAGGGGAC 177300
CTTGTGCCCC CTCCCTGCCT GTGCAGTTGG GGCTGAACCC AGCTACGAAG TTTGAGCTCA 177360
CTCTCTCCAG CTCCCTCTCA ATTCAGAGCT GAACTGTGGG AAGCTTCAGA GCTCTCTGTT 177420
TCAAGGACAG GTTCTCCTCA CCTCTCCTAA TGGAGGTGCA CCAGGGAACCT GGCCCTGCTC 177480
TGCCCAGGGC TTTCTCCTGG ACTTTGCCAT CATGGTCTAG CAAACCCTGT TCAGATTGAG 177540
GTGAGTGGTG AGATTTTCGA TTCTTTTGA CAGATAGGAT TAAGTCTTCT TCTGTGGGAC 177600
AAGTGGGAGG TAGAGGTAAG ATTAAGATG GCCAAATGTC TGAGTCCTGA CAGCCACAAT 177660
ATGGAGATCT AGACTTTTTA CAGACCACAG GGCACAGGGG CCTCACTAAC AGAGTTCCCG 177720
GAAGTGATGA GTGTGCTGGG GGCTTCCTGG TTGAAGAGAC ACTAGAATGG ACCAGCTGGG 177780
AGCTAATTTT TTGGGCTGGA GTGTGATGGC CTGCACATCA CTGCCTCTGT CCCTCCATTG 177840
TCACAGCTGC CCCTTAGGAG CCAGCTGAGG CAATTTGTGG TCAGAGTGAC TTTGCACAGT 177900
TGTCTGCCT GTGTTTCAGGA AGGGAGTTTC TGTGGTCCCT TTGAAACCAC AGAAGAGCCC 177960
CTCGTATAGC TCTCAATGGA GGGGGCAAAA CATTCAAATA ACTCAGGAGA TAACACAACCT 178020
ATTTGTTTTT AACTGTGAGT TTTTAGGCAA TCACAAAGAT CCAGATGTAT GTCCAAGCCT 178080
CTCTTTGCAA TTCTAATTAA CCTCAATGTT GCAACCATAG ACCTACCTTA CAGAGTTCAA 178140
AAAAATATGC AAAAACCTG CTTTCTTCT TCCTCATACC CCAAATGCC ATTCTGAACA 178200
TTTCTGTGA GTTAAAAAAA GATTTCCATG GTGTTACCAG GCACTGTACA CAGTCTGTGT 178260
CCCAAGACAA GGAGGTACAG TTCCACATGC GCCCATGACT GGGTTGGGCT CTGCACTCTC 178320
TCTATACTTT GAGAGCCTGA TTTTCTGTGA TTGGGCAGAG CTGGCCCACC TGGTGCAATG 178380
TCCTCCTCTG CCTTTCAAAC ATGTTTTAGT CATCAAGATC TTCAAATTTG TAACCCTTTC 178440
CAGCTTGATC CAGCAGAATG CAGATTTGGA AAAACAGAAC GAGTTTAAAA TACATGATTC 178500
TAAGAAACCT GGACCAGAAC TATCAAACT TGGTTTCCCA GAGAATATAG CAAATGGGCT 178560
CATTGGCCAA TACTATGACA TTGGCTTTTG AGAAAAGAAA GGCTTTATTG CAAGGCTGGC 178620
CAGCAAGGAG ACAGGAGTTG GGCTCAAATC TGTCTCCCA GTTTGGGGCT TAGGGCAAGT 178680
TTTAATTACA CAGACGCATT TCTTATGAGT AGCAGGCAGA GAGCCTCAA CTTCTTCTGC 178740
CTAGGTACCA GCAGCTTAGA CATGATGCAA ACCTGGGAAG CACATACTGT ATTTGGAGAA 178800
AGTGATTGGG AAGAAATGTG AGCTGAGGGG AGGGGCTCAG TGCCCCTGAG CTACACTTAG 178860
TGATGGCAGA GGAAGGATGT CCTCCGCAG GAGGCTGTTT CACATCTGCT CTGTTGTAG 178920
GGGGAGCTGG CAGGCATTAG CAGCGGCCTC TTTCCCCAA GAGAGGCAGC CTCCTCCAAG 178980
TTTTGGCGAC ATTATGGCCC TGCAATCATA AGGGTTTGTG AGCATAGTGC TAAGGAGGGA 179040
AATGGAGCTG CTGTTACTAG TTCCACCCCA ACACACACAC ACACACTCAC AAGAAACCTC 179100
ACAAGCACCG TATTGGAAGA CTTTGCCATC CAACCTGGGA TTTGACAGGC TCTAGAAGCA 179160
GAATCATAGA CTCATGAAGT TCCCCAAAG CAGGAATCTT CCTTACAGTA ACCCCCAACC 179220
ACCCCCCTCC ACCGCCTCCA CCGGCTGCTT CTTCTGAAC ACTGCAGTGT TTGGAAAACCT 179280
CACAACTTC CAAGCTTGCC TTTCTATTG TTGCATGGAT TGAAAGCTTG CGTTGTGTGA 179340

FIG. 6.68

AGAATGGCGC TTCCTGCTGT GCTTAGTTTT ATCTCATATA ATCTTTGCAC CATTTAATCC 179400
TTGCACTCAC CCACTCATGC AACTGCCTTT GCAGAGACTG GAGGGGCCGC TGTAGGCTGA 179460
CCTTTCCTTC ACTGTACCTA TTTTGTTCCC TGCTTTATTC CCCTGCACCC AGGACACTGC 179520
CTGGCACAAA GACAGGTCTT TATAAGTGTA TGCAAGTGAA TAAAGATATA TATATTATTA 179580
TTGTTATTTT TGAGACAGTT TCACTCTGTC ACCCAGGCTG GAGTGCAGTA GCGCAATCTC 179640
AGCTGACTGC AACCTCTGCC TCCCAGGCTC AAGTGATTCT CATGTCTCAG CCTCCTGAGT 179700
AGCTAGGACT ACAAGCATGT GCCACCACGC CCAGCTAATT TTTGTATTTT TAGTAAGGAC 179760
AGGGTTTCAC CATGTTGGCC AGGTTGGCCT CCAACTCCTG ACCTCAAGTC ATCCTCCTGC 179820
CTCGACCTCC CAAAGTGCTG GGATTACAGG CATGAAACCA GCCTAGAAAT ACATACTATT 179880
ATTTATCTT GTTTTACAGA TAAGCAAAGT GAGTCATGGA GAATTTGGTT GAAAGTCCCA 179940
AGGTCAGGAG TCGTGAAGCT GGGATTAAAA CCTAATCATC TGACTTTAGA GAGTAGACAC 180000
TTGCTCCATG CATATTGCCT CCAATTCATT CATTCAAGCA CTCCCTGCTC AAGAAGTTCT 180060
TTCTTATGTT GAGCTGAAAT CTGCAGCCCT ATGCGTTTTA CCCAGCAGTC CTGGTGCTGT 180120
TCCCTAAAAT CACTTAGACT GTGCCTGCTC TTTCTGTGTT TACAGTGTC A GCTGTAATAT 180180
CCCCCTCTTC GGCCTAACGT TTCTGAAGTC CCTTGCCACT GGGTCTCCTC TCCTCTTCCT 180240
GTGTTCTTTC TAAGAACACC TATGCAGATA GGTGTCTTCT GTACAGGGAA GCTGTTCCCTG 180300
AGATCCGGGC ATCGACTCTG TTAGAATAAT CTACGTATGA GTTATTTTTT TGAGAACTAT 180360
GTGTCATTGC TGA CT CATAT TAACTCTGTG GTTAACTAAA ATCTCAAGAT CTCTTTATGT 180420
TTGTTGAGAA ACTTATTTAA CTTCTCTGGC CCTCCGTTTC CTTCACTGAG CAGTGGAGTG 180480
ATTGATAACC TCCACCTGTG GTTGCTGAAG GTCTTG CACA AGATGATATA GTTAAAGTAG 180540
CTAGCAGTGC CCACGTACGG CGGATGCCTC ACAACGGTTT GCAGCCATCT CTCTATCTGT 180600
GTCTTTGTCT CTCTCTCACA CTGGTTTTGG CTTACTGTTA GCAGCTAGCC GAGATAAGTG 180660
TGTTTATGGT CTTTGCATGT ATTGTTTCTG TAGCATACTG GAGGATTACA AGAGGTTGGG 180720
GAGTGAGGGG GCGGTGAGGA GTAGACAAAG GCAGCCAACT CTCCAAGTT TAGCTTAGAA 180780
GGAAGGAGCG GTAAACCCTA GTTGAATGTT GGA CTGAAGC AGGTTTGTTT TTGTTTTGTT 180840
TAAAGGATAG GGAAGATCTG TCGTGTTTC CAGGATAAAG AAAAGGAGAG AATATGATAT 180900
TAAAGATTCT GGAAGTG GGA GAAGGAGCAA TGAAATACAG ACTTGAAGTC AGTGGCATGG 180960
ACAGGGTCAA GATCACAGTT AGAGGATGCA GCCTTAGAGA AAAGGAAGGG GCTCGGTTCT 181020
CTGAGCAAGG AGGGAAAGAA GAGAGGCAGA TGCAGAGAAG TACGGCACAT CGTGCTGCTG 181080
GTTGTAGAAA TAACCTCTGA CTTTAAATAA AGTCATCCCT CGGTATCCCT GGGGGATTAG 181140
TTCTATGACC TCCCTCGGAT GCCAAAATTC GTGGATGCTC AAGTCCCTGA TATAAAATGG 181200
CATAGTATTT GCATTTAACC TACACACATC CTCCATATCC TTTTTTTTTT TTTTTTTTTT 181260
TTTTTTTTTT TTTTGTGAG ATGGAGTCTT GCTCTGTCGC CCTGGCTGGA GTACAGTGGC 181320
TCGATCTTGG CTCACTGCAA GCTCCGCCTC CCGGGTTCAT GCCATTCTCC TGCCTCAGCC 181380
TACAGGTGCC TGCCACCACG CCCAGCTAAT TTTTTTTTG TATTTTTTAG TAGAGACAGG 181440
GTTTCACCAT GTTAGCCAGG ATGGTCTCGA CACATCCTCC ATATACTTTA AGTAACCTCT 181500
AGATAATCTC TAGATTACTT GTTTTGTCTT TTTTTTTTTT TTTTCTTTT GAGATGGAGT 181560
TTCACTCTTG TCACCCAGGC TGGAGTGCAA TGGTGCAATC TCAGTTCACT GCAACCTCCG 181620
CCTCCTGGGT TCAAGCAATT CTCCTGTCTC AGCCTCCTGT GTAGCTAGGA TTACAGGCCC 181680
CTCCCCACCC CCACCCCCCA ACAACTGGCT AATTTTTGTA TTTTATAGTAG AGATGGGGTG 181740
TCACCACGTT GGCCTGGCTG GTCTTGA ACT CCTGACCTCA GGTGATCTAC CCGCTTCAGC 181800
CTCCCAAAGT GATGGGATTA TAGGCATGAG CCACTGTGTG TGGCCTAGAT TACTTATAAT 181860
ACCTGATAGA ATGTAAATGC TATGTAAACA GTTGTTATAC TGTATTGTTA AAAGACAGTA 181920
ACAAGAAAAA AAATCTGTAC ATGTTCACTC CAGACAAATG GTTTTCTGTT TTTTTTTTTT 181980

FIG. 6.69

TTTTTAATA TTTTGGTCA GTGGTTGGTT GACTCCAGGA ATGCAGAACC CGCAGATATA 182040
GAAGGTTGAT TATGCGTTCA GAGGCAGGGA ATACCATCTT GGGTTCCAGA AAGAAAATGA 182100
TCAGCATTTT CTGTCATACT CTGGTAAAAA CAGATCTTTT GAATGGACAG GTGTATTAAA 182160
CCCTGTGGAG CTGGCTGGGC CTGGCGGCTC ACGCCTGTAA TCCCAGCACT TTGGGAGGCT 182220
GAGGCAGGTG GATCACGAGG TCAGGAGTTC GAGACCAGCC TGGCCAATAT GGTGAAACCC 182280
CAACTCTACT AAAAATACAA AAATTAGCCG GGCCTGATGA CGCATGCCTG TAGTCCCAGC 182340
TACTCGGGAG GCTGAGGCAG AAGAATCGCT TGAACCCTGG AGGTGGAGGT TGCAGTGAGC 182400
CGAGATCACG CCACTGCACT CCAGCCTGGG CAACAGAGTG AGACTCCGTA TCTAAAAAAA 182460
AAAAACAAAA ACCTGTGGAG CTGATGAAAT CCTGCAGGGA GCTTCACGGT GACAGCAAGA 182520
GGAGAAACAC ATCCCCATAT GCCCCGCAGA GTTTGAAGTC CCGGCTGCAC CTCTCCCCAG 182580
CAGCAGGTTG ACTCTGGAAA GTTGCAGCGT TCTTACCTAC AGAGTGGGAA CAGTACTACC 182640
CATTGCACAG AGTGGGTGCA AAGCTCTGTG ACGGAATACA TGGCAAGTGC CCACCACATT 182700
GCCTGGGATG AGGTGGGCCC TTCCTTTACG TAAGAGAGCC CTACAGATAC ACTCAAAGTG 182760
GGCACATTCC TACAGAAGGA GTGTTATTTG TGTAAGAAAAG AAAACATGA AAGGCTTTTA 182820
TTCCTATACA CAATAAAGCA CCCCTTTAAT GTCTTTTGA GGAGGATAAT ATGAAATTGA 182880
TGAAAAGGAA CCCTGTGGTT GGATCCCTGA CAATCACATG TATCCCTTTT TCACTCTTG 182940
AAAAAGGAGT AAAGGAATAA AATAGAAGGG GAGAGGGGGC AGAGAGACCT TCACCGCCCC 183000
CCCCCACCC CCCATCATCC AATCTATAGT CAAACCCTCC AGACTGTGTC TCCTTGGCAT 183060
CTCTGACACC CCCACCGCCA CCACCCAGT CAATTCCTAT CTTATCCCCC TATCCTGGAT 183120
CTGATTCTGC TAAGTTCCTG CCACACTAAA GACAGGGTGG CTTTCTGATG ACAACATTCC 183180
TCTGCTTAAA CCTGTCAGTA ATTCCTTGT GCTCTCAGAC GGAACATAAGT TCTGAATTC 183240
TTCACACGGC TCTCAGCAAG GTCACAGTCA CCCTGCTAGG CCCCAGGGGC AAATCTCAAT 183300
GGTCATCTTC TTGAAGACCT GGCTCAGTTA TTTCTTTCTC ATTGAGGCTC ACGACCCAC 183360
CTTCTTGCAT GCCTCAAACG GCCCCTTACC ATGCTCTTCT TTCGCCATA GCTCAGCACA 183420
CCATATCATT TTAATTTATG TATTTTGCTT AATGTGGATG ATCTGTCTCC TCCTCTGCTG 183480
TCCTCACCAG AGCATCAGTT CCTCAAACCA AGGCTCTTTG TTTTGTCTT GGATGCAAGC 183540
TAAATGTCTG GCATGTGGCA AATGGTCATA GATACATGTC ATTGAAAGAA TGATTCAATCA 183600
CCTCCCTCTT TGGCCTTGTC TGTGGTTCTA CCAATCCCA TTCCCTCCCC AGTGCCCTCC 183660
ATTCCCCCTC CTTGGCTGAA CATTCTGAAC CACAGACAGT TCTTACCCT GAACCTTTC 183720
ATATTTTGTT CTCTTAGCTT AGAGCGGCCC CTCTCCCTCC GTCTGCTTGG CTAATTTCTA 183780
CTTGTCTTC AGATTTTATC TTAGATGTCA TTCCCTCAAG GAATCCTTCT GTGACTCAAC 183840
ATGGAATTAA GTTGCCCTCT TTGACCCTGA AAGCACCATG TACTCAATCT CATCTTGGCA 183900
TGACTCACTT TGCTGTGTGG AATGTCTGCT TTCCTTGTTT GTCTATTCCT TTAGACTGTA 183960
AGATCCTAGA AAGTGGGGGC CGTGCCCTTG TCATGACTGT GTTCTAACA CCAAACACAG 184020
TGTTCAAGTAG AGAGCAGCTG CTGAGTACGT TTCTGCTAAA TGACAGTTGA TGGAGGACAT 184080
TTAGGGTTGC TTGGAGGTCA AGTCAAGGAG GCATTTAACA TTCTAGTAAA ACAAGGAAGT 184140
AACAGGCTCC TGAACATGCC CACAATGAAC CAGATGCAAA CCTTTCCCT TGGCAGGATT 184200
CTTTGCCCAT AAAGTGGAGC ACGAAAGCAG GACCCAGAAT GGGAGGAGCT TCCAGAGGAC 184260
CGGAACACTT GCCTTTGAGC GGGTCTACAC TGCCAAGTGA GTCCTAACCC TGATGTTGCT 184320
AATAAGTGGG GGCATGGGCA GGGGGGCCTC CTTCTAGGAG TGATGACCAC CCTTAATACC 184380
ACATGTCTGT CTGAGCCAAG TTTCTGAGCG CCAGGGAGGT GAGGAAGGTT GGACTTCACC 184440
AGAGAGGCTT TGTGGACACC CTTTATCATC TTAGTGAGTG CTAGTGCAA AACAAAGGGA 184500
GTGGGGATAT GGGGCACATT GGTGGAGGGA GGTGTGATCT CTGCAGCTTC AGAAAGATCT 184560
GAAAGAGTCA TTTGGTTAGA GAAGTTGACC TATTCCTGT GGGGTTAGAC CAGGTTGCT 184620

FIG. 6.70

ACTGTGAACA CCAGCCATGA CTCACCAGTC ACCTTCAGAA GCCACAGGCA GGACATGCTG 184680
ACGACAGCCT TCAACTCACC CACCCCTTGC TCCCCTGCGG GTGGAAGTCT GGAGGTGACA 184740
CCACTGCATT TTCTAACACG GGGGCTCCTT GAGCAACTAG AACAAGAACA GAAAGAATGG 184800
GGACATTAGC AGGTGCTTTC CCCCTCTCTC ATTCTTTTCT TTGAATAAAA AGGTTGTTTG 184860
AAAACACCTG AGCGGCTCCT AAAGATGGGT GCAATCTATT CGGGATGCAA ATCCGAATGA 184920
ATGTTATTCA AATGCTCCTC TCTTCTTTAT GCAGAGTGTA TTTCAAGGCT CAGCCAGTGG 184980
CAGGCATGCT GGGGACTATG GACTACGGAC TAGGGGCCTG TCACAGAGGA AGGCCTCATG 185040
CTAGAGAGCT AAGGGAGGAG CTGGCCTTCA GTTCCATCCC AGGAGCAACT TTGATGTTCC 185100
CAGAGATCCT TCCAAAGGGG GAGTCATGGT CACCCAAGAA AAATGTATTC AGAATGCCAA 185160
GAATGGTGCA AACTCAGGAC AAAGATTAC ACTGCAGGGT TGGAGTCCCT GGGCTTGCTG 185220
CTGGCACCAT GGGAGGGAGG GTCCCTTCA GGGGTACCGT TGGTTTCCTG TGAATTAAC 185280
TGGCTTCAAG GGATCTCGAC TGAACAGGCC TATATCACAC TCACTGATAT ACTCTCTCTT 185340
CAGTCCCTTCT CCTCATCTAG GTATTTTAA TTGTTTCAGT GAGGTGTAGG CATGAGGGGA 185400
TTGGAGGGGG CATCTCCTCC ATTGCAGTTT TTCATTGGCT GCTTTGCTCC CTCAGCTCCG 185460
AAATCGCTGG GCCACTCTCG AACGCATTAG TACGGTAGTC ACAGGTTGAT TGCCTGGCCC 185520
CTTGCCCTCT GTGGGCATTT TCCCTTTCAG ACAGCCCCTG AGTACTCACA GTGCTGCTAC 185580
AGTGGGCCAC CTAGATCTCC CTCTTTCTCC ATGCTCCAC GTGCTCTGGG CTCCACTCCC 185640
TTCTCCAAG CACTTCTGTC CAGGGCTATT CCAGCAGTCT GACCTCAAGG AAATCCTTTG 185700
CTAACTGAT TATAGAGAGG TTTCTATTTT AACATTTAGG TCTTCCATGT ATTAATTCTC 185760
AGAATCAATT TAAGATGTTT AAAGGTGTGA TTTAAGACAT TTTAAAACCA TTTGGAGGAG 185820
AGTACAGAAA TTATGTCACT TGCTGTCAGC CTCTTTCAC CATCTGCAGA GAAAGATACT 185880
AGAGTCCCGC CTTGGACACA TCCACATGCA AGAGGTGCAA AGAAGGTGTC TTTGATGAGG 185940
CAAGGTCAAA ACTTCTCCCC AGACGAAATC CAAAGAAAGC ATTCCTACTA TGCTATATCA 186000
GTTTGGAAG AAAAATTCT GCCAGGTGAC TGCATTCTCA CTGGTCACAT TGTGTTCTA 186060
TGGACTCCTC AGCTCAACCA ATTTGGAGAA GTTATGGTGC AATTCACCA TATCTGGTTA 186120
GAAGTTAAGT TTCCAATTTG CTGGCAATGA AGAAGAAATG GAGCAGGCCA GGCTGTGTAG 186180
TTTCTGCCAC GTGCCCCCGG GAGTGAACAG CTCTGTTTGT AAGAAGCCAT GGTGCTTAGA 186240
CCTGGGCTCG CTAGTTGCCA GCCTCCAAAT TGCAGAAGTG CCCTTTGGTT GGTGGCTATG 186300
CTGTGTCACT TGGGAAGGTC GTTTGGAAGT TCCACAGTCG TTGTGGGGTG CCAGAGATTA 186360
AAAAGCGTAA GAGGAGAGTG GAAAGTGATT GTTGCTGCTT GGGCATCCCC ACCGTGTGGG 186420
TGCTGCAGCC CAGCTCTCAA AACCCATGGG TCTGTACACT CAACCTCCAT GAGAGGGAAG 186480
GAGAAGGATG AGGGAGGGGA GAGATAGCCA TGGAAAGGTA GGAACCTAAGC AGGCAGGGTG 186540
GAGAGTTTTT TGTAAGACAA AAAGTGTCTG GACACTGCTG CGGTTCTGTT ACAAAGACCA 186600
CTTCCTCCCT GGGCCAGCAA CATATCTGTG TGCCTGTCTG GGTGTAAAA AGGGTCAAAG 186660
ATCAATGCAG CAGGCAGCTA CATGCTGGCA AAAGCCAGAG GCAGCTGGTC TGTTTGCCTG 186720
TGCCAGGAAA CCACTGGGAA TGGGGTTGTG TGTTATTCTA GGAGAAAGTC GTCCCAGCAG 186780
CAGCTTCTCC AGGGGCATCC AAGAGCACTG AAAAGGGTTG CAAGATGACC CATGAGGCTG 186840
CAGGAAGAAA AGAATGATGCA TTTAATCTTG CTATCTGAAA AGTAAGACAT GAAGCTTTCC 186900
TCATTTTAA TATACACATG GACAGTAGTA TGTGTATATA GTTTATATGC AAATATACTT 186960
GTTATAAGGT TGCATGCTCA AAATTTTTTG TTCATGGGGT GTGGGATCAT AAATGTTTAG 187020
GGACCATGGC TATCAAGGAA AACAGCATG AAGGATAAAT GATACTGGTG GATTAAGGAG 187080
ACAGATGCAT GTATTTTATG CATAAACAC AACTGCTGAC TGATACAGAT AGCTCAAGAT 187140
TCTGGGGCAG CTGCTGAACA GATACACTAG CCAGTGTGGC TCATCGGCTC AGACTTGGCC 187200
TTAATTAATG GGCTGTCCCT CCACCCATCT CCCATGAGGG CAGAGCTGAG CCAGGGTTTG 187260

FIG. 6.71

AGAGCTAAAA GGAATTGGAC CTGGACTCTG TTCACGTGTA TATTTTAATT CTAATTAATT 187320
CATTCTTTTG AAAGACAGAG TCACACTCTG TTGCCTAGGC TGGAGTGCAG TGGCACGATC 187380
TTGGCTCACT GCAACCTCGG CCTCCCAGGT TCAAGTTATT CTCCTGCTTC AGCCTCCTGA 187440
GTAGCTGGGA TTATAGGCAC ATGCCCCCAT GCCTGACTAA TTTTGTATT TTTAGTAGAG 187500
ACGGGGTTTC ACCATGTCAG GCTGGTCTTG AACTCCTGAC CTCAGGTTAT CCACCCGCCT 187560
TGGCCCCTCA AAGTGTGGA ATTACAGGTG TGAGCCACCG TGCCTGGCCT GTTCACATGT 187620
ATAAACACA GTTTAATGTC CTATTCCCAG CCAATGAGCA TGGCTAGAGC AGCCTTGGTC 187680
AAAGTTTGGT TTTTGGAGAA AAATCCTTGT TAGCTGACCT AAGATTCTC TTTGTGAGTG 187740
TAAGTAAGCA CAGGTTGCAG AGAGGAGAAG GGTCTCTGGA GAGGTGTAAT TTTCTAAATG 187800
GATTACAAGT TCATGGACTT TTAACAGGTG TTACAGGGGA TAACAAGTTC TTTATAGACA 187860
GACTTTTGAG GACGTTAAG GGTATTCTGA TTCTTGGTTT TCTAAGAGGG GAATGTATTA 187920
TTTAACTACA GACACCCCTA CCGCCCACTT TTTGCAGAGT GTATCAAAAC ATGTTTTTGG 187980
AATACCACCC TCATGTCGCT TCTCCCTGCA TCTCTTATCT CTTGGTGTCC ATTCTAGACT 188040
CACTTTCTTT CTGTTTTTTA TTTTATTTT TTTTGTAGAT GGAGCTTCAC TCTGTCACCA 188100
GGCTGGAGTG CAGTGGTGCA ATCTTGGCTG ACTGCAACCT CTGCCTTCCG GGCTTAAGCA 188160
ATTTTGTGC CTCAGCCTCC TGAGTAGCTG GGATTACAGC ATGCACCACC ATGTCCGGCT 188220
AATTTTGTG TCTTTAGTAG AGACAGGGT TCACTATGCT GGCCAGCCTG GTCTCAAAC 188280
CCTTACCTCA GGTGATCTGC CCGCCTCGGC CTCCAGAGT GCTCAGATTA CAGACGTGAG 188340
CCACTGGTGC CTGGCCTAGA CTCACTTTCA AGTGGCATAG ACTTGTAATAA TTATTTAAAG 188400
GTGATAGGTC TACAATGATC CTGTCAATTA GTATTGACAC TATTATTAAT AAAGTGTAT 188460
TAATTATATT TACTACTTT AAATTAATCC AAATAATTA ACGGAACACT AAAGAGTTTC 188520
TATGTTTTAT TCCCAGAGGT GGAGAAAAAT GAAAGGGAAT ATAGCAACGA ATTCTTTTCT 188580
CCATAAAAAC ATGAATAGTG CAGCACATCA AGTTGAACAT ACCACAGCAA ATTGTTGCAA 188640
GATCTGCTGA GTAGCTCCTA TTTAGACCTC AAGGAATGAG ACTCAAAATG GGTTCATCAG 188700
TTCTGTTTTG CAGAAAAAAT AGCGCAAAAT TTCTCAAAAG AAAATCCAGA ATAATAATAA 188760
TTTGTCAATA GGAAAGACAT TTCCACTGGG GGTTAAGAAG GAAGACATTG GAACAATGAT 188820
AGCCACCACT TATTGAATGC TTAAGTGAG CCAGGTGGCA CTTACCTTG TTTATTCTC 188880
ACAACAGTCT AGGGAAGTAA TTAATAATGT CTCCATCCAC CTCTTGTA TAGACAACT 188940
GAGGCTCATT GAGGCTAGGA AATGCACCCA CACTCACATA GCCCATAAGA GGCAGCCATG 189000
GCATTGGGCC CAGACCATGT GAACTTCAAA GACTACACGA GCAGCCACTG GGCAGCTGTC 189060
ATGGCTAAAG CCACTTGAAT TCAGCCCAGC AGCAACCCCT TCTCCAGGAG GGGCACATAA 189120
GCTTGACAGT TTGGGTAGAA GCTGCACTTG AAGTCCTGGA TGGCGAGAGG GACTGGCTTG 189180
AGCCAGAGCC AGGAACAAGG CTCTGAGAAT ATTCTGGAAA TCCACAGGAG GAACCCATT 189240
TCTTACAGCT GGGAGAATTT CATTCAACTC CAGGCTGACC ATGTTTTATT AGGAACGAAG 189300
GTGACTTGAA CTAATAGTCA GGAATGGTTG AATACGGACC CAATGTCAA TCACTAGGCA 189360
GTTACATTT CTAATGAGCA AATCCCTTAG ACAATTAAGA ATTTTTTTCC TTTTGCATAA 189420
CCCAGACAAA ATCGCTACTT AAAACAAAC CAAAGACCCG AAACATGAGA AAGAGAAGGA 189480
AGCAGGGGAA ATCTTTGGTA CTAATAAGTT TTTAAACAAT AAGAGCACCA GATATTTTAC 189540
CCCATCAGAC ACAGAATGTT ATTGGAATAA CCAAAAAAGG AATTTTTTCT CTAAGTTTCT 189600
TGAAGTGAA AATGAATCAT ATTTTCTCAG TCCTGAGGCT GCAATTTTGT GCCTCTAGTA 189660
ACATATAAGA ATAGATGTGA TGCCAGTGCC CAGTAGCTGC TGCAATTGTT ACTTGGGGAC 189720
CTGTTTATTC ACTAAGCACT TCACCCAGT GATAAATTTG TAGGGGCCTC CTGCCCTTG 189780
GAGCTCCTAC CGTGTCCATT AGATCAGTGG AAATTCTGGG ATTCAGAGCA CTTTGCAAGG 189840
TCAGCAGGGG TCTGCTCTTT CTGTCCTGTT CCTGGTTTTT GGTGTGCCT GGATTCCAGG 189900

FIG. 6.72

GTAGGTTTCT CATCTGTTAC CTTTCATAGAC TTCTCCAGAA AAGGATCTTT TGACCATCAG 189960
AGGACCACGA AGATTCCATT GGTGAGGCGC AGATAACCTG ATCTCTCTGG GTTCTCTGCA 190020
GGGCACAGAT GAAGGGCTGG CCATTCCCAA GTTCTCAGTG GTACCACTGA GGCATGAGAC 190080
CCTAATGGTT TGCATGAGCA GTTTGAAAAT TGCATCTTTG TTTTACCTA TATAATCACA 190140
TGAAACCCGT GGTCTCAAA CGTCAGCAGG CATCAGCATC ACATGGAGGG CTTGTAAAA 190200
CAGATTTCTG GGCCCAACA CAGAGTTTAA AATTCTGAAG GCCTGAGGTG GGTGTGAACA 190260
TTTGCAATTC TAACATGTTT TCGATGCTGC TGCCGCCTCT GGTCCCGAGA GCATGCCTGG 190320
AGAACTGCCA CCTTCGACCA TGGACTGTGA GAATTCACAT GGACCTCAGA ATTATAATCA 190380
GTCTCTCAGT TTTACAGATA AGGAACTAA ATCCAGAGAG ATTGTTTTGC CAATGGTGAA 190440
CAGCTGGTTA AAGTCAGGAT GGAGACTTTA ATCCTAGTCA AGTGACCTTT CCTCTGTATT 190500
TATTTCCCTC CCTTTTATG CCTCTCAAGT CTAGTTACAC TGTTTTTCAT GGATGGGCAT 190560
ATTTATTGTC CTGATCTGGA CTGCAGACTT CTCAGGAGGA CACCTATGAT TTAATTTAGT 190620
ATAGTTGAAG AGTTAACAGA CATGGCTTTG GAGACAGACT GATTATGGTG TGAATCCCGG 190680
CTTTGCCACT CCTAGCTGG ATGACCCTGA GCAAGTTATT CAGCTTCTCC AAGCCTGAGT 190740
TCCTTATTGG AAACATGAGA GCAATTGTGA TAGGCAGAAT AATGGCCCCC TCACCAATCA 190800
TGCCACATC CTAATCCTAG GAACCTGTGA ATATGTTATG TTACATGGCA AGGGGAAATT 190860
CAGGCAGCTA GCCAGTTGGC CTTAAATAA AGAGATTATC CTGGATGATC TGGGTAGGAC 190920
CTGATGTAAC CACAAGGGTC TTTTAAATGT GGAAGAAGGA GGCATAAGAG TAGATGTCAG 190980
AGTCATTCAA AATAAGAAAG ATTTGATGGG CCATCCCTGA CTTTCAGGTT GGAAGGAGGT 191040
TCTGAGTCAA GGAATACAGG TGACCTCTAG AAGCTGGAGA AGGCAAGGAA ATGGTTTCTC 191100
CCCTAGAAGT TCCAGAAGGA TTGCAGCCCT GCTAATATCT TGACTTTATA GCCCTTTGAG 191160
ATTTATTTTG GATTTCTGAC ATCCTGAACC ATAGTAAAAG GGTGTTTTTT GTTTTTTTGA 191220
GACAGAGTCT TGCTCTGTTG CCTGGGCTGG AGTGCAGTGG TGTGATCTTG GCTCGCTGCA 191280
ACCTCCGCCT CCCAGGTTCA AGTGATTCTC CTGCCTCAGC CTCCTGAGTA GCTGGGATTA 191340
CAGGTGCTTG CCACCACACC TGGCTATTTT TTGTGTTTT AGTAGAGACA GGGTTTCACC 191400
ATGTTGGCCA GGCTGGTCTT GAACTCCTGA CCTTGTGATC TGCCTGCCTC AGCCTCCCAA 191460
ATTGCTGGGA TTACAAGGCG TGTTGTTTTA AGCCACTCAG TTTGTGGCCA CTTGTTACAG 191520
CAGCAAGAGG AAATCATAC AGTTATCATG TGAATCACA GGAATATGGT GAGTTAAAAA 191580
GAGAGGAAGG GTGCAAAACA TCCACGGTAG AGTGAGAACT CTCCAGGGAG TGAGGACTGT 191640
GCCCAGCATA CAGTGATCAC CCTCTTAGTA AGCTAAGTTT CTGAGCACCA GCTTTTTTGA 191700
GTTGACTTTG TTGTCTTTAA CATTTGAAGA TCACCTTCTT TTGCTCAGCC TGGCTTGCA 191760
ACCTGGGCTG ATTTGTGGAT CTGATAGAAA AGTTTCCTTA GTTGGGCTCT TCTCCCCGAC 191820
CACCCCATG CCAGTGTGGC CACATCCTCT GTCTGCATTG CTCACTCTTC AATTCCAAGA 191880
AGCGCAGGGG CACCGCCAGG AACAGGAACC CTGCCAGAGG AATACATCAA GAAACCAAGT 191940
CTCCCTTACG CATCACCGTA GGAACAGAGT TAATGGATTA TGAACATGTG TTTGCTTTAT 192000
ACCATTGTTT GTTTCCAGG TGGCAGCTGG CTGCCCCATC TTATTGGGTA GATGTAAGTG 192060
GAATTACGAA TGGGATTTAT GTTTCATGCA CGATGGTGAT TATTAACCTC AACTTTCAGG 192120
TAATTTTCAG ACCACATTGC ACTAATTGG TCTCTGATTG TTTTCTCCT TGTTTGTTA 192180
TTCTGCAGCC AGAACTGTGT AGATGCGTAC CCCACTTTCC TCGCTGTGCT CTGGTCTGCG 192240
GGGCTACTTT GCAGCCAAGG TAACTCAGAC TTCCCTTTGT TCATTCTCCT TCTATAAAGT 192300
GCATCTCAAG GAGGTTCAAA GGGCAGGCTT TTTGTTGAAA GGAATTTGCC TGACCTCTGG 192360
CTCCCATCTG TGAAGCCCTG GAGAGGTGAG AGCCCTCGGG AGGCCGTGTT TCAGGCATGC 192420
TCTGCACCCG TGCAGAGCGC GTGTGATAAT GCATTGCTAA TGCTTGCTCC CTGGTGGCTG 192480
GCTGAGAGCT GCTGTGCTGA CAAGGGTGGT TTAAGGCTAA ATGTGACTCA GAATCCTTAA 192540

FIG. 6.73

GCAGTGTTAG TTCAGATACA AGGGCATTAT AAATGAGAGT GCCTGAGGGA TCTATTTTGG 192600
GACCGCTGTC ACTTGGCTCT TCTGCTAATA AGCTTCCAGT GTGGTGGCCC TCCTTCAGGC 192660
ATGTTTCCAC TGAGCCACGG GCTGGATGCC ACATCCCCGG CCTTCCCACA GTTATCAGCA 192720
GCCCACAGGC TTGACTTGAG CAAGTTGGAA AGACAAATCA ACTTCCAGAG TTGATTAAAC 192780
ATTGAGTGGA AATCAGTCAT ACTTTTGGTC CCCTTTCGGG GCCACGCCTG GCACTGTGCC 192840
TGGTGGCAGA TCGGCATGAA CTGGCCAGCT TCTGTGGCCC TGGAGGGCAC AGGCAGAAAG 192900
GCCCACTCA GTCCCATGAT GAACTGTTTA AGACTTATTG TTGTCTCCCC GCTCTGTAAA 192960
GTAGATAGAG TGGATTTTAT GTCCCTTATT ACCTTTCAGG ATACTTTGAC TCAGGGAGAT 193020
AAAGTAACTT GGGTACAGCT ACTCAGCTGG TGAAGAACAC AGGCAGAATG AGTGCCTGGG 193080
TCTTTTGA CT TAAAATTCTG GATTTTTCAC AAAGATCCTC TTA CTTTTATT CATTTACATA 193140
ATAAATATAT ATTGAAGAGC TACTCTGTGC CAAGCCCTGT GCCTAGATAT ACAGTGATAA 193200
ATAAAGAGTA GCTTCTAGAG GTCACCTGGC GGTGAGGCAC AGGCCAGCTG GCAAGATGGA 193260
CCACAGAAGT CAGTGAATGA AGACAATGAC AAGGGTGGGA AGCGCCATAT GGAAGAGAA 193320
CCAAGTTCAG TGATAGAGAG CAGAGGTGAG GCGGCAGCAG AAACCACTTA AGGGACACCA 193380
CGTGGCACTC CTTCTGTGCT GAGAAGGCTG TCAGTAAGCT CACCATTAT TCTCTATTTT 193440
CTCTCCTGAG TTAAATAGGA AACATGTCTC GCATTACTTG AAAAATCAAG TCAAATATG 193500
CTCTTACTAG GAGTTATGGT TCTTTTATG TCTTAGATGA TGCTTGATCT AGATGAATGC 193560
GGACTTGCTG TAGCTAGATA AATACAATGG GAGTTTGAAG GTGTTTCGTA GCCCTGGAAA 193620
TAGGTATTTT CTGTCAAAAC AAGCTTTGTC ATTGCCAGCA GACAAAAGCA TCAGTAACCT 193680
TGGTTGATAA TCGTCATTTT TTAGGAATAA AGTAGACTGT AGAATTTTTT TTAGCAGAAA 193740
GGAAACCCAA AGATAATTCT AGTGCAAATC CCTCACTTTA TAGAGCAGAA GCTCAAGTCC 193800
CAGAGGAACA AGTGGCTTGA ACGAACATCA GAATTTTAGG GGCTGGATTT GTACCTCCT 193860
GGTGCCAGCA GCCCACTTCC CTGCAGGAGG CACTCACCTT CTTGCACAG GGGTATGAGT 193920
GTGGCCATTT TCCACCCATA ATCTCTGTTA GCTCATGTTT AATTGGGTTT CCATTGAAAG 193980
AAAAATGGAC CAGTAAGTTG GAGCAGAATC ATTCAGATGG TATAACATAA GGAAAACTT 194040
TGCCCAAGGC AAATCGTGAT TGTGACAGCT TTGTGATTTT TAGAGAATAG CATGGGCCAG 194100
GCACAGTGGC TCATGCCTGT AATCCCAGCA CTTTGGGAGG CCGAGGCAGG CAGGTCATT 194160
GAGGTTGGGA GTTCGACAAC AGCCTGACCA ACATGGAGAA ACCCTGTCTC TACTAAAAAT 194220
ACAAAATTAG CTGGGCGTGG TGGTGATGC CTGTAATGCC AGCTACTCGG GAGGCTGAGG 194280
CAGGAGAATC ACTTAAACCT GGGAGGCGGA GGTGCGGTG AACCAAGATA GCACCATTGC 194340
ACTCCAGCCT GGGCAACAAG AGTGAACTC CGTCTCAAAA AGAGTTCACA GTTTCTCTTT 194400
TGCTTTGATT TTCTTATCTG CCGGATAACA ATAGTATTTT GGAAGGCAGG AGGAATTGTG 194460
GAAAGAAATG GGTTTTGGGG AGTGGCTGAT TGGAGGCAAA TCCAAGGACA CTCATTGCTG 194520
GTGTGTGACT CCAGGCAGTT ACTCAGCTTT TCCAAGCCTC AGTTTCCTTA TTGTAAAACA 194580
GGACCATGGT CTAGCTAGTA GCATTCTAT GGTGAGTGAA ATAATATGTA TAAAGCTCCT 194640
GACACAGTGC TTGGCATATA TCAGATTGAG CCATGTAAAA CTGCCAATAT CTGGCTATTT 194700
ATGACCTACA AAAATAGCAT TTCATATGAT TCCACCTAAC ATCTGAAGCG CAATAAATGT 194760
TATTATTGAT AATGCAGGTG GTGGTGATAA AGTTTTGAAA TCAGAAAGAC CTGGCTTCAA 194820
ATTCCACGCC TCACTGGCC TGACTTATTT TCATTCATTT GACAAATATT ATTTTGAACA 194880
CCCCATGTG CCAGGCACTA TGCCAGGCTC AGAGATGATC TAGGAAAAAG ACAGATGTCC 194940
TCATCTGTCT TAGGCTCTTG TGGCCTAAGC CTAAATTTCC TCGTCTGTCA AATGGTGACA 195000
GTAACACACT CTTACCAGA GAGCTGGGAG GATTGGAGAC TCAAGTTCCC AAAACGCCAG 195060
GAGCACTGCG GCAGGTGAAA AGTATTCCTT CAATGGCGGA AGTGTTTAAA TTGCTTTTAT 195120
ATCTGTAGCT CTAGATAACA CTAGTTCAG CTTAGTTAAC TCCCAGCTCC AAGCCTTCAG 195180

FIG. 6.74

GACTTCATAG AGTTATTGGG GTGCTGCTCT TGGCAGTTTC CCAAAAAGCT AGAATGCAGA 195240
GGGAATCTCC TTCCCAAAAA GCTAGAATGC AGAGGGAATC TCCTTCCCAA AAGGCTAGAA 195300
CGCAGAGGGA ATCTCCTTCC CAAAAGGCTA GAACGCAGAG GGAATCTCCT TCCCAAAAGG 195360
CTAGAATGCA GAGGGAATGT CTTCTCTTC TAAATGGTAG CTGTTAGTTC AAGAAAGGTT 195420
AAACATTGTG CTGTGGGGAG GCTCAGGGGT GAAGGGTGTA CTTTAAAGAG AACCAGTTTC 195480
AGAGCTGGGT TTGGGGTTTA AGCCCTACCC TCTGCCCCCT TTTACGAGCT GACAGCCTTA 195540
TGCAAGCCTG GTTGACCACC TGAACCCACG TTTCCACATC TGGAAATAGA AATGTGGGTA 195600
CTAGTTATGT TGAAAGGACT CAGGTTAGAT GATAGATATG CAAATACCTT GGAAACCAGG 195660
AGTGTCAGT CTTTGGGT CCCTGAGCCA CACTGGAAGA AGAGTTGTCT TGGGCCACAC 195720
ATAGAATACA CTAACCCTAT CAATAGCTGA TGAGCTAAAG AAAAAACGTT GCAAAAAAAA 195780
TCTCATATTT TTAAGAAAGT TTATGAATTT GTGTTGGGCT GTATTCAAAG CCATCCTGGG 195840
CCACGTGCGA CCGCAGGCT CCGGGTTGGA CAAGTTTGTT GTAAACAATG CCATGATGCC 195900
GGCATAAGGT CGTTACCAGT ATTAGGAAGG TTCTCAGGTT TCCTCTAGCC CTTGGGCTCT 195960
TTTCTGAAG TCGTGTGTC TTCTGCTAGA TTTGTGACC AATGTTGATT GCCTAATTGG 196020
GCTAACAGCA TGTTTTGGTG GCTACGAAAC TGACACAGGT GTTTTCATTT CTCCACTTAG 196080
TTCCTGCTGC GTTTGCTGGA CTGATGTA CTGTTGTGAG GCAAAAGTAC TTTGTGCGTT 196140
ACCTAGGAGA GAGAACGCAG AGGTAGGTAA CTGGGACTAC TAAAGAACTG TGGAGCGATT 196200
CCTGATTTTT GAGCAGGAAG AGTGACAATT CAAACAGTA TTTGACTAGA TTCACGGCTC 196260
CGTAGCATCC CTTGGGTGG GAGGGGGAAG GCTGACTAGG ACCTCTGATT CTTCTTTCCC 196320
TGAGCTTTGA AGGCTCTGAA AATACAGCTG GGGGGACTTG CCCAGTTTTC TTATTAAGCA 196380
ATTCTCCGC ATGGTGCTGG CTTTCAAAGG GTGCTTCAGT GCTGTTTGCT GCACGTGCCT 196440
TGCAGCCCCA CACCCTGCAC TCCCGCCCTG CAGAGTCTGG CGCTGGAATG ACATTTTAGG 196500
TCTGGGTTCC CAGGCCTCCT GAGAGTGAAA TGTTTCATTG TTTGTCTAGA GAAATGAGAA 196560
CTAAAGCTTG CACCTTGTA TAAGTTGTCC TGAGGAACAT ATCTTTCAGG GACCAGAAGA 196620
AAGAATGTTG GGAAAATAAG ATGCAGTAAG ATGCAGACAT GACAGCAGGG TGCAGCGGCT 196680
CACGCCTATA ATCCCAGCAC TTTGGGAGGC TGAGGTGGGT GGATCACCTG AGGTCAGGAG 196740
TTTGAGACCA GCCTGGCCAA CATGGTGAAA CCCCCTCTCT ACTAAAAAAT ATACAAAACA 196800
TTAGCCAGGC ATGGTGGTGG GCGCCTGTAA TCCCAGCTAC TCCATAGGCT GAGGCTGGAG 196860
AATCGCTTGA ACCCAGGAGG CAGAGGTTGC AGTGAGCCGA GATTGCGCCA CTGCACTCCA 196920
GCCTGGGCAA CAAAAGCAAA ACTCCATCTC AAAAAAAAAA AAAAAAAAAA AAAAAAGAT 196980
GCAGACACGA GACTGTGAAA CTGACTAGCA TCACCATTGC ATTGTTTATA GATGTTGCCA 197040
GACAGAAAGC CCCAAAGCAG CACAGTACCT TCCTGACATC TGGACTAGGA AATCTAGATT 197100
TTAGTAAAT ACATGCTAAT ACTTACAGAA GAAATGTCGG CGTTAGAGTA TGCCGTCAGT 197160
TCCTTAGAGA TTGCAATTCC TAATGCACTA GTATGGTTTC AGGTGCCAGG AACACGTTCT 197220
GTGAGGCTGC TGCCCCAGGT GCTGACCCCA GCCTTCCACA CCATTTTCCT TCCTTGTTGT 197280
CACAGCCGCT CTGTCTTTTA CAATAGCACC CCTCTCTAGT GGCTAATGGG CTCTATGATT 197340
AGATAGCATC CTTAGTAGT GATAAAGGCA GTGACATCCT AGGGAGGTCA GCGGGTGAAA 197400
GCGCTATATC TGAAAACCT GAGAGCCTGT GAAGCTCAAG GACTTGACGG GGTTAGACCG 197460
TGAGCCGGGC TGCAGCTGGA AAAAGAATGA CTGTTCTTTC AGCAGATCCT TCCCTGTGCC 197520
ATCTCTTCT TCATTCCTCT CTAGTGGCAT TCTTATTTAT CCTCTAAAC CACAATTCCA 197580
TTATCTCTCC TATTCCTATC AACACTGCCC TAAATGATAT TCTTATTCT CTTTGGCCCT 197640
GGAAAACCTC TATCATGCCT TTCCCATGT GATTACCTCG TTAAGAGTGG GGGTGGAAATG 197700
TCTAGCAATG AAATAAGAGG GTCTTCTCTT TTGCCTGGCT CCCTATGCAG CCCTATCTTA 197760
CCCCCTGCAA AGTCCCAGGG ATGTGGCTCA GTCAGTGCTC CTCTCTTCAT CTGTCACCAC 197820

FIG. 6.75

TTGCTTGAGA TCCTACAGCT GCTTTAATTC CGAGACCATC TGCAGAACAT GACAAAATTT 197880
GTCCACCTAC CCACATGTCC TTTAACTTT AAAGGCTTTA CTAAGTATT CCTATTAGGG 197940
AATGAACAGA GGTGGCAAAA ATAAACAATA GGAGATTGAT TTACAAGAAA TCTTTAAAT 198000
AGTAGATTTT TCGGACCTC ATTGAAATAT AAATGGCCTG CTTCTTTGTG TCCCTCCCTG 198060
GTCTCCCTCT TTAGGTGATA AGAAGAAGAT CCTGCCAGCC CCATAACCCG CCATCTGCGC 198120
GGGTTCTAGA CCCCCTTCTC CTCCCCTCTG GCCGTGGTAG GCATTACTGA TGAATCATGG 198180
TGCTCTTTCT TCCAGAGACC AAACCTGGCC TCGGAATCCT TCTTAACACA GATACTGCTT 198240
AACACAACCA CTCTGAGCAG CTGTCATAAG TAGAAGTAAT AGATACTAGA AGAAATGTCT 198300
AAGCCTAATC TAGACCAAAA TACGGCCTGA TATAGATGCA AGCCAGAGGG GCTTTATGGT 198360
TAAATGCAAG GAGATTTTCA ACCCTGCCGT CTAGAAGCTA CTTGCTGAGA TCTTCTTCAG 198420
TTGGGCCCCAT CTCCTCCCCA GGCCTCTCTT CTGTTCTCTG GCTATGTCAC ACTTGACTC 198480
TGCAGACACC TAATGCTCTT GGGACCTGCT TTAGTTCTTG ACCTACCAA CCGAGGAGGA 198540
ATTGCTAGAT GAGATCCTTC CCCCAGGAATT TCTCTCTTGA ACCCCAGATG GTCCGTTGCC 198600
CCTTTCCAGA AGTTGCTCCA GCCCTGTCCG CTTAGGAAGT TCAGTGTCAT CTTGATCCA 198660
GTGGGTAGGG AAGACATTCC ATAATGAATG CCCAGTCTG AGCTTCTTCC TTCAGGCTTC 198720
AGGCTGCCCT GCGAGGATTT TGCAGCTCCC TTTTAAATGC CCTCTAGAAG TTTCTGGCTC 198780
TTATTTTCAG CCCTTCATCC TACTCTCTCT GACCCCTTCC TCTATCCTGT TTAGTTCACC 198840
TGTAGCAGTT ACTACCCAGC AGTGAAGGAT GAATCTTGGT TTCGTTTCTT TTCTCTTCTT 198900
TTCTTTTTTC TCTTCTCTT TCCCCTTCCC TTCCCTTCCC TCCCTTCACA TCACCTCATC 198960
TCACCTCACC TTACATAGTC TTGCTCTGTC ACCCAAAGT GAGTGCAGTG GCCTGATCTT 199020
GGCTCACTGC AACCTCCACC TCTTCCCAGG TTCAAGTATG TCTTATACCT CAGCCTCTTG 199080
AGTAGCTGAG ACTACAGGTG TGCACACCA CACCCAGCTA ATTTTTTGTA TTTTAGTAG 199140
AGATAGGGTT TAGCTATGTT GGCCAGGCTG GTCTCGAAGT GCTGAAGTCA AGCAATCTGC 199200
CATCCCCGGC CTCCCAAAGT ACTGGGAGTA TAGGCATAAG CCACCCATGA TGCCAGCCT 199260
GAATCTTGGT TTCTTCCCCA TTCATTTAAG CTATTACCTG GGCCTGAAGT CAATGGCACC 199320
TGGCACCAAC TGGCAACTGA CTCTTGGTCT TTTATTACCT ACCTTCCCTA GCAGGCACTG 199380
GGTTGCTCCC TCTTCCTATC CCATGGAGTC CTGTCCTCTG TTGGGGCTCC TACTGATCCT 199440
CTTGGAATA TGAAGTTCTC AGCTCAATGG TGGGTGGGCA ATGACTGCCA ACTCTTGAGG 199500
CCAATGAAGT CAGGTTACCC CACTCCTCCT CCTCTGAGT TGCTCACTCA CTCCTCATTC 199560
ACTCAACATT GATTCACTAG ATATTTGCTA CTTGCTCTGT GCCAGGTACC AGGTCAGTTG 199620
CTGAAGGAGT AACAGTGAAC ATGACGGAGT CTTTGTCCCC AAGGAGACCC AAGGTGTCTC 199680
CTAGAGCCAG GGGCACATTG CAAGACCAAA TATATTC AAC TACCAAAAT AATCATAGAC 199740
CTAGTTCTCA AAAAGCAAGA AGACTGATTC CTCGTTGTCA TTTCTCCTCC TCAGCATCAA 199800
TGTTTTAGAG TCTGTGGGCC CCTCCAAGTG TGGAGTATGG TGTTACTTCA CCAGAGTTTG 199860
AGGAGAAACA TTCTTCTTTT GGAAGGCCGG GGAGCATAGA TGGATATCAA GGCTGCTGTT 199920
TCTAAAAGCG AAACCCACCA AACAACAGTA TTAGAATCAT CTGTGGTGCT TATTAAGAT 199980
ACAGATTCTT GGGCCCCATC CCAGACTTAT GAATCAGAAT CTCTGCCAGA GGAAGCCTGA 200040
GAATTTGCAT TCTCAGATGA TTCTGCATTC TCAGATAACA CATTCTTTAG GTGATTCTTA 200100
CACACACTGG AGTTTGGGAA TCGCTGAAGG CTGTTCACTT CTCTTTTCTG AGAAATGATT 200160
CATTCAATTC AGAAATATTT GCAGAGGTCC TTATTTATTG GAGATTTGTG GGTGGGCAGA 200220
GGAGAAATAT CTTGTCCTCA CAGAGCTTAC AATTTTTATT TTCTTTAGAG GTCACCAGGC 200280
TTAAATGAC ACTTCCCTAA ATTCTGAAAA GAACAGATTT TTAACAAG AAGGGACTGT 200340
AATGTTTTCT GTTCTACCT CGTATTTTGT TCACATTAAG AACCTGGGGT GGGAAGTGGA 200400
GGAGGGGGGG TGAAGGCGG GGGGCCACAG AGAGCTGAGC TGGGGTGGTC TCGAACTCCT 200460

FIG. 6.76

GAACTCAAGC AATCTGCCAG CCTCAGTCTC CCAAAGTGCT GGGATTATAG GCATGAGCCA 200520
CCCACGATGC CTGGGTGGAA CTCAGGGCTC TGGATGCCTG GGCGCCCCCA TCTCCCACAC 200580
TACGGCGCCT CATCCTAGAA GTGGTTAGCA CCTTTGAGAT GGGGAATTATT TAGCAGGATG 200640
CTTTTGTGTT TTCATGTAAG TTTTATGCTG CCTGTGGAGG GCACAGCTGT TTCAAACTA 200700
ATAACCAAAT CCTGGTCTCC GAAGTCTGAA GGCATCCTTT GCCCTGCAGT GCAAAGCACG 200760
GGATTCTGGC CTCACACAGG CAGGTCTGAA CTCCTGTGTT GCCTCTTGCT GGCTGTGGGA 200820
CCTGAGGCAA ATCATGCAAC CTCTCTTTTC TGTTTGCCTA GATGGAAT AGGTTTACAA 200880
TACGCCCCCA TAGGATGGCT GTGAGAATTA AAGGAAGTCA TGGGTGTACA ATACCTGGCC 200940
CCGAAAGATG CTTAATAATT TAATTCTGAC CTTCCTCACT CATTAGGAT TATGTACCAA 201000
CTTTTAGAAA CAATGAAAGA TTAGTGAGTC TTCTGTGGTT GGTATAAAAA AAAAATAGAA 201060
ACATGAAAGA GATGTCCTCC TTGTTCAAGG GCTAATGACC CTGGTGTGCG CTGTCTAGGC 201120
CCCCAAGGTC TTCCTTCCCT GCTCACAGCA TTTCAGGTTT TCCGCAGCTT TGCTGAGCCT 201180
GGGTCAGGTT CGGTATCTGC CCACCATGCT CACTTGCCAC AGCTGTGGCC CCATTTCCAA 201240
ACTTCAGAGA CTAAAGGTG CAGCTAATGA TGTGCCCGGC CTGGGGTCAC ATTCCTGAG 201300
CCCTGCAGAC AAGGGAGCAG GAGGCTGAGC TCTTATCTTC CACACCCTGT GCACAGCCTG 201360
GGAAGAGTTA AAGCACCTA GTCCTATGCT GCGAGGGCCA CATGCCCTGA GACCTTGGA 201420
AAAATCCTAC CTGAATTGAA GAGCATCACT ATTTTCATCAG GAGGCGCTGC CATTTTCTT 201480
TTCACCTCGG TTTTATCTTG AGTGTA AAC AGCTTCGCA ATCACTTTT CTGTTTCTG 201540
TAATGAGCAT ATGGTGGCCT CATTCTGTG ATAAATCTGA GCCACCACGA TATTTGACTT 201600
TTCACAATTT AATTTATCTG AACCTCTAT TCTCTGGCTA AAAAATATCC CTTACTTGGA 201660
CTTCTTTATT TTATTTTCAA TTCCCTTACC AGCACTAGCA GGGGACTCTG TACTCATCTG 201720
CTGGCGCTGC CATAACAAAG CACTGCAGCC TGGGGGGCTC AAACCACAGA ATTTATTCTC 201780
TCACAGTCCT AGAGGCTAGA AGTCCAAGAT CAAAGTGTGG GCAGGGTCGG TTTCTCCTGC 201840
AGCCTCTCTC CTGGGCTTAT AGAGTGCCAC CTTCTACCTG TGTCTTCACA TCATCACCTC 201900
ACTGAGCATG TCTGTGTCCA AATCTCCCT TCTTATAAGA CCCCAGTCAT ACTGGATGAG 201960
GATCCACCCA TATGAGTTCA TTTTACCTTA ATTATCTCTT TAAACACCCT GTCTCCAAAT 202020
ACAGTCCCAT TCTGAGGAAC TGAGAGTAAA GATTCAACAT ATGAATTTT GAAGGGACCT 202080
AATTCAGCCC ACAACACCCT CTTTGGGAT GTTTATTTT CCCCTTAAGG AGCTAGTTAG 202140
GATGTCTTAT CTCATGAACA TGAAGTGAA CAGGAAAACA GGGAGAGAAT GAAGCTGGCC 202200
AAGGAACAGG GCTGGTGTCA GCTAGCAGTG CTTTCTGAT GTGAGTGGGT CCCACAGGGA 202260
GCTTGTTAAA ATGCAGATTC TGATTCATTA GGTTCAGAG GGACCTGAGA TTTCCCATTT 202320
CTGACAAGTT TCCAGTGTGG GGGCTGATGC TGCTGGTCCA CGGACCATAC TTTGAGTAGC 202380
AAGGAGCTTG ATACATAATG GCTGAGTGAC TTTCAGACTC CTGCTGTAGA AAAATTATGA 202440
GTTGGCTGGG CGTGGTGGCT CACGCCTGTA ATCCCAGCAC TTTGGGAGGC CGAGGTGGGC 202500
AGATCACCTG AGGTCAGGAG TTCGAGACCA GCCTGGCCAA CATGGTGAAA CACCATCTCT 202560
ACCAAAAATA CAAAAATTAG CCAGGTGTGG TGGCAGGTGC CTGTAATCCC AGCTACTCAG 202620
GAGGCTGAGG CAGGAGAATC GCTTGAACCC GGGAGGCAGA GGTTCAGTG ATCTGAGATC 202680
GTGCCACTGC ACTCCAGCTG GGCAATAGAG CTTGACTCAG TCTCAAAAAA AAAAAAGAA 202740
AAGAAAAAGA AAAATTATGA GTTATATTAT CAGCATATGG GGTGCCTTTC AAATTGATAA 202800
AATTTCTAAT ATTAACCTG TGGATGCCAA ATGCTGCTCT CTGATTATGG CAGGAAACGG 202860
CACTTGGCAG TACGAAGTTA GCTGTTGGGC TGAGCTGGCT CATCTTGTTG TGCGGTCCTG 202920
ATTGCCTAAA GATGCCCTCC CAGGATCTTT ACTAACAATC CTCCTGAGTC ATTTGGACTT 202980
TCCCAACCTG TTATCACCTC TCAGATGGGC CAGCCATGGA GGCAGTCAGA GGAGGGCTCT 203040
GCAGAGGGAG GGCAGAAACA GGGTGGCCTC TGCATGCCAT TAGGAGGTCA CATCTCACTG 203100

FIG. 6.77

GGGGATGCAG TTTAGGATTT AGTGCCTTGG AGAGAAGGAT AGAGTATATT AAAACATGTC 203160
TCCGCTAGGC ATGGTGGTTT ACGCCTATAA TCCCAGCACT TTGGGAGGCC GAGGTGAGTG 203220
GATTGCCTGA GCTCAGGAGT TCAAGACCAG CCTGGCTAAC ATGACGAAAC CTCATCTCTA 203280
CTAAAATACA AAAAGTTAGC TGGGAGTGGT GCGTGCGCC TGTAGTTGCA GCTACTTGGG 203340
AGGCTGAGGC ATGAGAATCA CTTAAGCCCA GAAGACTGAG GTTGCACTGA GCCGAGATTG 203400
CACCCTGCA CTCCAGCTTG GGCTACAGAG TGAGACTCTA TCTCAAAAAC AAAGAAACAA 203460
ACAACAACAA TAACAACAAA AACCAAGTCT CTCCCTCCAC TCAAAAATGC AAGGGCCTGT 203520
CTCCCATTCG TGGGTGCCCA GGTCTCATGA ATGTAGATAT GAATTATTCC AGTCAGCCTC 203580
AGGAGAATAG AATGAGCCCT CAGATGCCGA AGCACCTTTC AGATTCCACC GGTTTTATCG 203640
GCTCATTTAA ACTTCACTTC TAACACAGTC CTGCATTACA CACGTGTCTG TCGTTATGGG 203700
CAGCTGCAGA GAGGGTCTTA ATGGTCCTAA TGCTCAGTGA GGATGCCCAA TGGTCAACAG 203760
AACCTGCCAT CTTCAGGCCA TCAAGGAGCT CTGGAGTTAA GGAAATCATG AGAGCACAGA 203820
GGGGCGGGTA CAGCAGAGCC CTCGTGGTAA TGGGTTTTGA GGTCTAGGCT CTCTTCACTT 203880
GGGTTTAAA TAAGTTCAAT GACTAGTAAT AGCTGAGACA CTTCTACCCT TCAATGAAG 203940
TAAATGGGAA AATGGAGCAT TGTTGAGTCC AGGGAGCTAT AATTTAAACC CCATATATCT 204000
AAAAGGGGTA ACATTTTTGT GTGTGTGAAA TTGGTGTCAT TCGCACTGCA TCTACAGTTT 204060
TCTTTTTCCT TCTCTCCAG CACCCCTGGC TACATATTTG GGAAACGCAT CATACTCTTC 204120
CTGTTCTCA TGTCCGTTGC TGGCATATTC AACTATTACC TCATCTTCTT TTTCGGAAGT 204180
GACTTTGAAA ACTACATAAA GACGATCTCC ACCACCATCT CCCCTCTACT TCTCATTCCC 204240
TAACTCTCTG CTGAATATGG GGTTGGTGTT CTCATCTAAT CAATACCTAC AAGTCATCAT 204300
AATTCAGCTC TTGAGAGCAT TCTGCTCTTC TTAGATGGC TGTAATCTA TTGGCCATCT 204360
GGGCTTCACA GCTTGAGTTA ACCTTGCTTT TCCGGGAACA AAATGATGTC ATGTCAGCTC 204420
CGCCCCCTGA ACATGACCGT GGCCCCAAAT TTGCTATTCC CATGCATTTT GTTTGTTTCT 204480
TCACTTATCC TGTCTCTGA AGATGTTTTG TGACCAGTTT TGTGTTTTCT TAAAATAAAA 204540
TGCAGAGACA TGTTTTAAGC TGATAGTTGA GGGGTTTTGT TAATGGCTTT TGGGGGATTT 204600
ATCTCTATAC CCACAAACGA CTAGTTTGTT TTCCTCAAAC TAAATGATAA TATTA AAAAAT 204660
ACACATCCTG GCCAGGTGTG GTGGCTCATA CCTGTAATCC CAGCACTTTG GGAGGCCGAG 204720
GCAGGTGGAT CACTTGAGGT CAGGAATTAA GACCAGCCTG GCCAATATGG TGAAAGCCTG 204780
TCTGTACTAA AAATACAAAA ATTAGCCAGG TATGCTGGTG GATGCTTATA ATCCCAGCTA 204840
CTTGGGAGGT TGAGGCAGGA GAATTGCTTG AACCCGGGAG GTAGAGGTTG CAGTGAGCCA 204900
AGATCATGCC ACTGCACTCC AGCTTGGGCA ACAGAGTGAG ACTCCATCTC AAATTA AAAA 204960
AAATACACAT CTGGCTTCTG GAAAAATTAC TTGAAGATCT TTTATGACAT CCATCCCTCT 205020
TCACACAGCC ATGTGAATTA GGTTGGTATC TTCATATACT AGCATCGTGC CCAGCACTTC 205080
CATGTTATAC AGTTTAAAT GTTCTGTAAT TCCCTGTGGG AACCTAAGAT AATGCGAGGA 205140
CCGTCATACG TGCCCCCAA TATTGGCAA CCAATGAATA AATGAATGAA TGAGTTTATG 205200
AATCGCTAAC TGGCTGTATT TAATGAAGTA TGTGTGTTGA GCCATTTCCC ACAGTGTGGA 205260
CAGATTTGTC CCACAATATG GGCCTCTTCC CAAAGGCCCT ACCACCTAAT GCCATCACAC 205320
TGGGGATTTG ATTTCAACAT GTGAATTTGG GGAGAGTGCA AACACTCAGA CCATAGCACC 205380
ATCTCAGTAA ATGTCCCACT GGTCACCTCAG TTCATAGTGA CAGTGATCCA GCCACTGTCA 205440
TGACAGGTGC CACTTGGCAG AAACAGCACA GCTTGGAAGA TGGCGGGGTG TAGTCAAGAT 205500
TCCAGGATCC CCAACAGAGA AGCCAGCTCT TATAGGGGAG CCATTCACTA GGATTGA ACT 205560
CTCAATCGAG CTGGACAGTA ATAGGTGGGT CTGTGTTATT CCCAGATGA GTATCATGAC 205620
AGTCACAATC CTAGGAAGGA TGTGAAGCCT CCCCAGCTC TCCTCCAGTT GCCTGCTTGG 205680
GCAGCAGAGA TGATGGAATG TGGAGTCTGG CGTGGTCTGA GGCCTGAATC CATGTGCCTC 205740

FIG. 6.78

ATGTATGATG CTCAGGCAAG AGGATCTCTC AATTC AAGGG AGAGGGCCTG AATGAGCCTT 205800
GCTTTCCAGG CCTGTCTGAT GGTCCAGGCT GAAGCCCCCTC CTGGCTTGCA CTGCCAGACC 205860
TCATCCAGCA GGAGCTCCTT GGCATTGACT GCTTCAGGAT AGTTGCTTCT GCTCTGAGTG 205920
CTCTCTAAAG AGCAGTGCTC TACCATCCAA GCTGGGCTTT TCTTTTCTTC TTGCTGATAG 205980
GGAAGGCATG GGACATTGCA GGATGGAAGT GGCCCCCAGG CCTTCTCATG CCTGGGCTTG 206040
GTTTGGAAGG TGGTCAGGTG ATCAATAATC CTGATTGGCC TGGCATTGAG GAGTTTTCCCT 206100
GGGATGTGGT CCTTTCGGTT TTTTAAAAAT TATTTTATT GATACACATA TTTGTAGGTA 206160
TTTGTGGGGT GCATGTGATA CTTTATTATG TGTGTGGATT GTGTAATGAT GAAGTCAGGG 206220
CATTTAGGGT CTTTCATCAC TTGATTATCA TTTCTATGTG TTGAGAACAT TTCAAGTTCT 206280
CAGTTCCAGC TATTTTGAAA TAGACAGTCC ATTTTGTTAG CTACAGTCAC CCAACCCGGC 206340
TGTCAGACAT TGGAACCTAC TCCTATTGAA CTGTGTATTT GTACCCATTG ACCAACTCT 206400
CTTTGGGCTT TCAGTTTTAC AACTGGGATG ATCCTGGGAA AACTAAAGTA AATCAGACAC 206460
CCGACGTGTG AGCTAGGTTA TAATATGCCC AGTGGACCCT GGGGACATCT TAGCTTTCAG 206520
AGGTCATGCT GTCCAAGCTG ACTGTGGGGC TTCCAGAAGG TGGGGAGAGG AAATGATGCA 206580
ATGGCCCATC AGAGGCACTA CTTGGGGCCT GGGGCCAGAG TGCATGTCTA AGGCATTAAG 206640
GGGAGGGGAG AGCAGCCTTC ATAATTATGA AGAGGAGTCT CAGGTGCACA GCTCTGATG 206700
AGGGACAGCT TCTAATTGAA GACAGCATTG TGTAATGCTC AACTCCCTG TCTTCAGAGT 206760
GCCTGCTGTA TCCCACCATC AGTTCTGTGA CTTCTCCCTA AGCCTCAATT TTGCATGTGT 206820
TACATTGGGA TAATAATAGT GCCAACTCA TGGGGTTGTG AGGAATAATG AGGTAAAGCA 206880
ATTGAAAAGG TTAGCACAA TATAAGTGCT CAATAAAAGC CATTATTATT ATTTTATTAC 206940
ACTAGTTTTT AATTCCTGCA TAGCAAATTC TTGCAAATGT AGGGACTCAA AACAAATATA 207000
ATTTATTATC TGACAGTTTT TCTGGGTCAG AGGTCTTACT AGGCTGTAAT CAGAGGGCAA 207060
CCAAAGCTGT GATCTCAGCT GAAGCTCAGG ATTCTCTTCC AAGCTCACTG GTTGTGTGCA 207120
GAATTCAGTT CTTTCCAGTT GGAAGACTAA AGCCTACAGT CTTCACTCTC TAGAAGCCTT 207180
TTCTCTGGCA CAGGTTTCTC TACAACATGG CCATTTATGT CTTTAAGGCC AATAGGAGAA 207240
CATGATTAGC ATATTTTTTT TAAGTGAAGT TTAGACCTT TTTTAAAGGC CTATCTGATT 207300
AGGCCAGGCC CAAGTGAGCT TTAAGTCAAC TGATTAGAGA TCTTAATTAC ATCTGCAAAG 207360
TCCCTTCATG TTTACCGTAT AACATAACTT AGTGAAAGGA GTGAAATTGC AACCAGGTTT 207420
TGCCTGCACT CCACGGAAGG GGATTCTGCA GAAGTGTGGG TCACGGGGGGG GTTATTTTGG 207480
GATTCTGCCT ACGTCACTGA GTCAAAAGAA GCTGAATGGT TGTGATGCTG AGGTTTTTGG 207540
GCAGCAGCAG TGTGTGTGTG TGAGTGAATT CATACGTATG ACCACCTGGG AAGAAAGGAG 207600
GCTGTGGTTT CCTCCACCTC CTGGCAGACA GAGAAATTTT TTTTTTTTTT TGAGACAGGG 207660
TCTGGCTCTG TTACCCAGGC TGGAGTGCAG TGGCTTGATC TCTGCTCACT GGCTCACTGC 207720
AGCCTCTGCC TCCCAGGTTT AAGTAATTCT TGTGCCTCAA CTCCAAGTAG CTGGGATTAC 207780
AGACACACAC TGCCACGCCT GGCTAATTTT TGATTTTTTA GTAGAGACGA GGTTTTGCCA 207840
TGTTGGCCAG GCTGGTCTTG AACTCCTGAC CTCAAGTGAT CCGCCACCT CAGCCTCCCA 207900
AAGTGCTGGG ATTACAGACG TGAGCCACCA TTAACCATTT TTCTATCTCC TGTGGGAAAG 207960
GGCACAGTGA AAGAACAGAT GAAGCTGAGA CATACAAGTG AACTCCTCCC TCCTCTCCAT 208020
TTAGACTAAA ATAGGATTAT TCATACTGAG ATTCTCCCTG GTTGCAAAGA GATAATCTGT 208080
GCAACTGGGT TTTTACAATT ATCCCTACCC TATGCTTTCC TCATCTGTCT TCCTCGTAGT 208140
CAGCTCAGGC TGCTATAACA AAACACCATA ACTGGGGGCT TTTGAACAAC AAAACTTTAC 208200
TTCTCACAGT TCTAGAGGCT GGAAATCCAA GATCAAGTTT CTGGCAGATT CGGTGTCTAA 208260
TGAGGTCCTG CTTTCCAGTT TATAGACAGT GCCTTATCGC TACCGCCTTA CACAGTGGAA 208320
GGAGAGGACG AGAAGCTCCT TGGGCTTTTT TTTGTTTCTT TCTTCTCTC TCTCTCTCT 208380

FIG. 6.79

TTTTTTTTTT TTAATAAGGT CACTATCTTA GTCCATTTTG TGTGCTAAA AGGAACATCT 208440
GAGGTTGAGT AATTTATTTT ATTTAAAAA GTGGCCAGGC ATGGAGGCTT ATCCTGTAAC 208500
CCTAATCCTT TAGGAGGCCA AAACAGCAGG ATTGTTGAG GCCAGGAGTT CAAGACCAGC 208560
CTAGGCAAGA TAGTGAGACC CCATCTACCC CATCTCTACT AAAATTTTAA AAAATTAGCT 208620
GTGTGTTGTA AAGTGTGCTT GTAGTCCCGG CCACTTGAGA GGCTGAGGTG GGTGGAGTTC 208680
AAGGCTGCAG TGAGTTATGA TTGAGCCACT GCACTCCAAC CCGGGTAACG GGGCAAGACC 208740
TTGTCTCTAT TTAATAAAAA AAAATCTTTA TGTGGCTCAC TATTCTGGGT GGCTGGAAG 208800
TTCAAGATTG GGCATCTGCA TCTGGTGACA GCCTCATGTC GCTTCCAGTC ATGGGGGAAG 208860
ACGAAGGAGA GCTGGCACGT GCAGATATCA CGTGTTGAGG GCAGAAGCGA GAGAGAGAGG 208920
GGAGAGATGC CAGGCTCTTT TTAACAACCA GCACTGGGGA AACTAATAGA GTGAGAGCTC 208980
ACTGACTCCT GAGGGAGGAC ATTAATCTAT TGATGAGCGA CCTGCCTCCA TGACCCAAAC 209040
ACCTCCAACG ATACCCACCC TCCAACACTG CCACACTAGG GATTAACCTT CAACTTGAGA 209100
TTTAGAGGGG GGAAACTTAC AAACATCGC AGGCACTAAT ACCACTCATG AGGGCTCCAC 209160
CTTCATGACC TAATCACTTC CTAAAGGCCT TACCTCTTAA TCTCATCACA TTGAGGATTC 209220
GATTTCAACT TGAATTTTGG GGGGACACCA ACATTCAGGC CATAGCATCA TCTCAATAAC 209280
TGTCCCATTG GTGGTCACTC AGGCCCAAAA CAAAGGAACC TTCCTCCATT CTTTCCGCC 209340
CTCCACCCCA CAGTCAATCA TCCCAAGCT CCATCAGCTC CACCTTTAAC GGCCAACCCA 209400
CCTCTGCCAC ATCTACCAT CTCCACTGCT ATCCCTGTCA CCTGGGCCCA CCATTCTCTC 209460
TCCTGGACAG TCTCCATAGC CACCTCTGTC AGATTTATTT TATTTTTTTA TTTTTTTTTT 209520
TGAGACAGGT TCCTGCTCTG TTGCCAGAC TGGAGTGCCA TGGCATGATC ACATCTCACT 209580
GCGGCCTCCA TCACCTGGGC TCAAGCAATC CTCCCATCTC AGCCTCCCA GTAGCTGGGA 209640
CTACTGGCAC CACCATACCT GGCTAATTTT TTGTTGTTGT TGTTTAATTT TTAATACAGA 209700
TGAAGCCTCA CTATGTTGCC CAGGCTGCTC TTGAACCTCT GGGCTCAAGT GATCCTCCGG 209760
CCTTGGCCTC CCAAAGTGCT GGGATTACAG GCATGAGCCA CCGTGCCAG CCCATCAGAT 209820
GTAAATGCTA CACGCACTTG CTTAAATCC CCCAGATAAT TCTCGCTGCT CTTGGAATAA 209880
TTCCACACA CTTGGCGTG GCCATGCAGG CTCTGTGCCA TCGGATATGT CCCTGCCCCC 209940
TCTCCCAACT CCTCCTTTCG CTTGCTCGTT CACTCAGTTC CAGCCACATT GCCCTGGGAG 210000
CTGCTCCAC CATGGGGCTT CCTAATGCAC TGGTCTCTCT CATGCAGTGG GGCCTCTCCC 210060
TCCTTTTACT CAGTGTCTCC CAGCACCCAC CTCCTCCAGA GCCTTCCCTG ACCACCACAC 210120
CTACACCTAG GCCCTTCCTC CTCCACGCTC CCTCCTCCAC CCCGGCCTCC TACCCACGTG 210180
TCACTTCTTT ATACTCGCTG CCACCTGAAA TTAGATCATT TATTTACCC TTTATTTGTT 210240
CAGTTTGCCT TGCCGTTAG AATATAAGCT TCAAAGGGC AGGAGCTTTG CCTATATTGT 210300
TAGGCCGGGC ATACAATGAG CACTCAAAAA AATATTTGAT GAGTGTATGA AAGAACAGAC 210360
TGGGTTATGT AATTGTGCCT ACTTACCTAT ATGACCGTGT GGTGGGGTTT ATGGTGGGTG 210420
TGGTGGTGAT GGCTATAGGG CTATAAGCAA ATTTGGGACA GGGAGTCTAA GAAATGTTCT 210480
TAAATTTTAG TAAGCAAAGC ATCCTCTACA GAACCTGTCT TAAACATGA AAGTTCCTTA 210540
GTGCTACCCC CAGAGGTATG ATTTGGTAGG TCAAGGATAG GGCCTGGAAA TTCACATTCT 210600
TGTTAAGATG TTCTTCATCC GGGGTTTGTG GACCACCTTT TCAGAAGATT TTTGCTCTGT 210660
AGCTGTACTA CCCAATGCAG TAGTTCGTAG TCAGTGTGGC TCCTGAGCCC TTGAAGTGTA 210720
GCTCCTCTGA ACTGAGACGT GCTGTAAATG TAAATTGCAC ACCGGAGTTT GAAGAGTTAA 210780
TACAAAGAAA AAGGAATGCA AAACATCTCA TTAATAATGC TTTACACTGA TTACATATTG 210840
AAATGGTAAT CTTGTAGATA TAGTGCGTTA AATAAAATAT ACTGTTAGGC TTAATTCAC 210900
GTCTTTATAC TTTAATGTG GCTACTAGAA AAATTTAAAT AACATATTCA GCTCACATTA 210960
TACTCCTATT GAACAGAGCT GATCTATAAG TTCCATGGAA GATGGCAAGT CTTGCGAGCT 211020

FIG. 6.80

GAAATAAAGG CTGGATCCCA TTCTACGGGC TCATCTTTAG CAATGATTTC TTGCAGACGA 211080
TATTGAAAAA TGTGGCAATG AAAGTTACCA CAAGCATCAA ACCAGTCCTG CCTAAATCTG 211140
GAAAATAGTT ATCTGAGGCT GTTAGCATAT GATCATGAGA GCGTTTCACC ATGGATTCT 211200
GATCACAGAT GTGGCACATT ATTTAAATAT CACTTTTACA GTCACCCTAG AGGCTAGGGT 211260
TATCTGAATA TGGAGAAAGA AACAGCTTGT GGAGCTGTTG TATAAATGAA ATTACTAGAA 211320
AGTAATGCAC TCAATTGCAT ATTGGCTCGG GGGGTTATTC TTATTAAAT GTTTAGAGAG 211380
GACTTTCTGT TCATTTCTGC AGAATTGCTC TTCAAATTA GAATTTGCTT GACACGCTAA 211440
TAGACCACAG TCCCAAGAGA AGTTTATCCT TTTTCTTCT TATCCTTGCT AAGCACTTAG 211500
ATGCTCTGCT GATAGGTAGC ATATATTGTC TATATGAAGC TTTTGTGTTA ACATTGACTA 211560
GTCCTGCAAG TTGGCACACT CTTACTTGGC CTAAGAGAAA TCAGCACCAG GCTTTAAGAA 211620
AATCAGATGA TCTACCTAAA GGAACACAAC TCTGTCTCTC TTTTGACAAT TGTTGTAAAC 211680
AAATTTTAAT GGAAATTTGC CTTAATTGTG AAGAAGTTGC TGCTAAATG GACTTGCCAT 211740
TAATGGACTG GAACCCATTG CATAAGCAGA ATGAAATATA AGCCTTCTCA GGATTCACAC 211800
TTATAAAAAA CCATTCAGCC AATCAACAAG AGGGCAAAAG AACAAACATT TGATGTGTAA 211860
TACTTAATT TAGTGCATAT GCATTTGGGT CCTCAATGTC AGCACTATGG CAACCAGAAC 211920
ATGGCCACAA TAACTGTCTG GAAATGTCTA TTCTTACCTG GACCCAGCAG GCCATGCCCC 211980
ACTGATTATA TAATCTCCCT CTCTCCTTGT TACGGTCTGA ATGCTTGCAT CCCTCAAAAA 212040
TTCATGTGTT GAAATCCTAA CCCCCAAGGT GATGATATTA GGAGGTCGGC CTTTGTAGAG 212100
GTAATTAGGT CATGAAGACA GCATCCTCAT GAATGGGATT AGTGTCTTA TAAATAGGC 212160
CCAAGGGAGC TCATTCACCT TGTCCACCAT GTGAGAACAC AGCGAGAGGG CACCATTAT 212220
GCACCAGGAA ATGGGCCTTT TCCAGACAA CTGTCTGGTGC CTGGATCTTG GACTTCACAG 212280
CCTCTAGAAC TGTGAGAAAT TAATTTGTTT TTTATAAGCC ACCAAATCTA TGGTTTTTTT 212340
TATAGAAACC GTAATGGACT AAAACACTCC CTAATTATAT TTAACTTAT CAGTGCCTG 212400
GGCAGTGACA TATTAAAAGA ATGCTGGCCA ACGTAATTGA CACCATAAGG CTGGATGATT 212460
CTTGTAATTT TCAGCCTCAG AAAAAGGCTG GGGAGAGGAG TCAGGGGAAA GGAGGTGGTG 212520
TGTGTGTGTG TGTGTGTGTG TGTGTGTGTG TGTGTGGTAC GGTGGATGCC TGCTGAGAGA 212580
GAAAGAGCTA TAATAACATT CTGTGGTTCA GCTGACACAT CCTTCTGCA TCCCCTCCAA 212640
TCACCTGGGT TAATGGGGAC CTCGCTAATG TCTGAACCTC ATCTCATTTT AACCTTTTGT 212700
TTCAAAGCCT CTCTTTTCAT GACTTCCCCG CCTTCATTTT TCCCATATGG TGGGGTTATT 212760
ATTAAGACAT TAAATGAGAG TGGACAGGTA GGCAAAGGAG GTGGGTTGCA GGGGAGTTGA 212820
GGGTTGCCTG TGTACTTTTC TAGACTGTTT CACTTCACAT CAGTGAAATA TTCCCAATTG 212880
ATACTATCAT GAAACAAAGC AAATGAAATG CTGAGCACGG AGCTTCGTCT TGATGAAATG 212940
CTGAAAGAAA AGAAAGGAAA AATAAAGTAG CCATTATTTT TGCCCTTCCT CCCACCCCCA 213000
TGTTTACTAC TCTTATTTCT CTTTGTATT GTTGTGTTGG AAGCACAGCA TCAGAAAAAC 213060
TCCCAGTTTT GAGAGATAAC TCAGTGTTTA GTTCACTTAA ACCTGAGAAA GGAGAAGAGG 213120
ATGCCACCGT GAGGTCCAGG ACGTAAAGAG GAAAAAACA GACAAAAAA TCCATATGAA 213180
ATGAAAATGT GAAAGAGGCG CTTTCGAGCA GATGAGTGTT GTAGATTACA GTGTTGAGAG 213240
CTGTTTGTGT CCAGAGCTGC TTGCTGCACC TGGCGGGATA AACACTGGTC TAACAGAGGA 213300
TCCTTGTTTC AAGGAGGCTG CCTTTTATTT GGGGGGACAA AATTGTTCTT GAAAGCTGCT 213360
CAGTGGTTCA AGCTACAGCA TGGTGGACTA GCAGAATGGA CTCCAGGGCC TCCGAGGAGA 213420
CAGTGACTGC TGCCAGAAAT AGTCAAGGAT AGAAAGGAAG GACTTCACTG AGGCCTGGGA 213480
GAAGATTATG GAATGGGACT GACAGCAGTG ACGGGGAGTA AAAGGGGGTG TCTGGGGGAA 213540
TTGTGCCCCA TGGTGAGAGC TAGAGGGTTC ACAAAGACTT AACCCGACGC ATCTCTCTCA 213600
CCCTGGAGAT TGGGCCCGTT CAATCTAACT GGATGGCTAT AATTTAAAAG GTTTAGGTAT 213660

FIG. 6.81

TATGACAAAC ATGGATATAT TAGGTGATAG CAATGCAAAA TGCATATGGC TTCTTGATAT 213720
AAAACACAAG ACTTGAAAGC AGCATCTTTG GCTGGGTACT ACAGCCACCC TCCTCTGTCA 213780
CTAAGGGAGG CTTTGGTGGA AAGGGCTGAG AGCCTCTAGA CTGTGAACAA AAGTAGGCAC 213840
AGAAGAACAG TTGGAGATAA TAAGTAAACC ATCTTGACAG GAATGAAGAA TTCCTGAAA 213900
GGAAGGTCCC TGAGTTAGGT TGTTGGATGC TTTCAGTAGT GAGTTATTGA AAGTGTTTGG 213960
GGGGTGTGTG TGTGTGTGTG TATGTGCAGT ATGTGTGTGT 214000

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FIG. 6.82

Figure 7

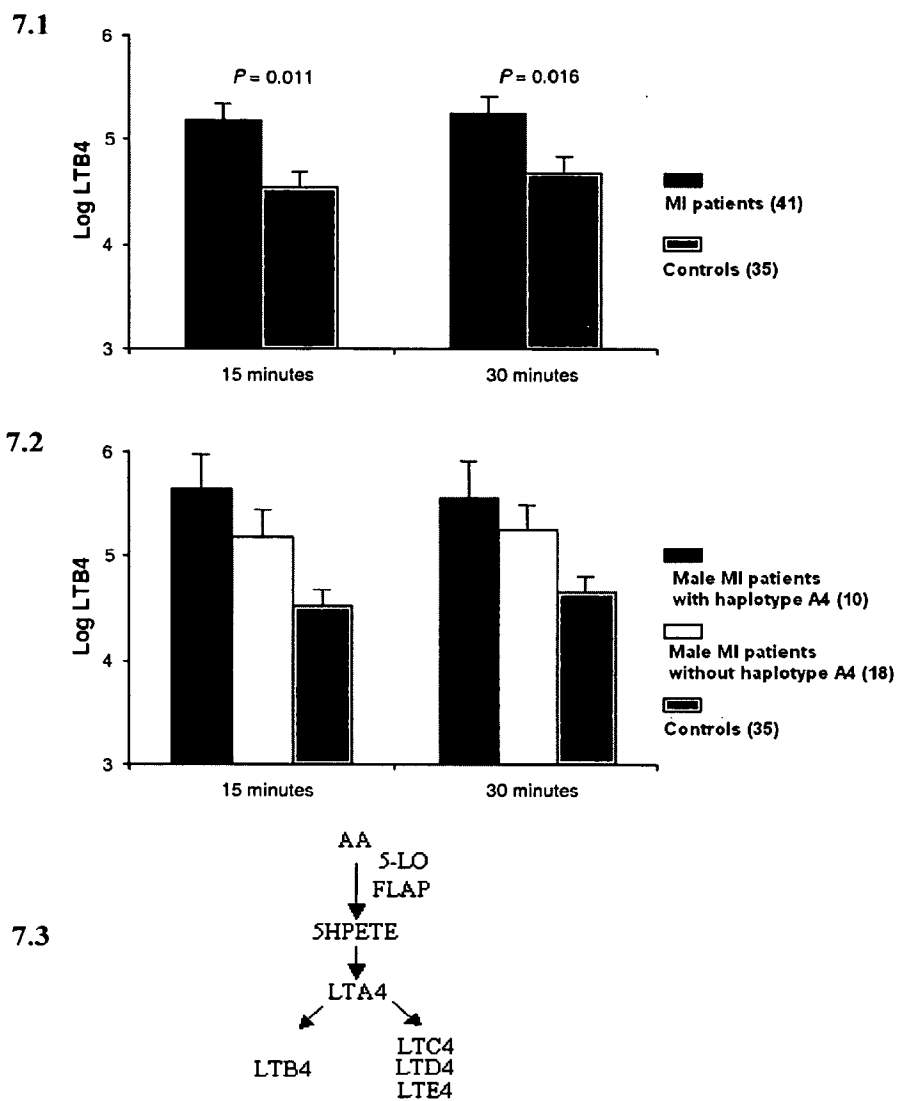


FIG. 7

SNP name SNP amplimers

SG13S421

GATTATATCCCACCTACCACTGCAGCTCCAGGATCCAGCTTCACAA
ACATTTGTTGAATGAATGAATAAGAAAAAGAGGACACCCCCAAAGAGGCT
GCAAGGGAAAAAGCTACAAAGACAGAAGCACCAGGAAAAAAGTAGGGTC
ATGTAAGTCAAAGCAGGAAAAAAGTTCCATGGTGGGGTGGTCAGCAGTGT
CTAAT[A/G]CCACGAAGGCACAAAGTAGGATAAAGGTTAAAAATCAGCCT
TTGGTTTTGGCAAATATGAAGCTTATCGGTAGCCTTAGCGAGAACAATTCC
ATCAGGGAGCAGAAGCTAACTGCAGTGGGTTGAGTCATCAAGCAGGCAT
AAGGAAGTAGGGATACCCCAATTATAAGCTACTCTTTCAAGAAGCTCAAAT
CTGAAG

SG13S417

ACAAAAATTACCATCATATGCTGTCATGCATGTCTGCCAGTCTATTT
ATCATATTATTTAAGAAACAAACATTTATTGAAGATTTATCATGTGCTCAG
CACTGCCAAAGAGGAAATAAAGAGCATAATATCTATTCTTAGAAAAATAAC
ATTAACACAAATAGAAAACAAGAAACCATAATGTAAAAAATATTACATAG
[C/T]AACACAGAAAGACAATGTATAATTATACATACGCACTAAAGCAAAG
ATAACATAATTTATAAATTATGAGGTACAGAATAGTTAGATTCTGAAAAT
TAAAAATAATCAGGAAAAAATTCATGAAGATGAGATCTGGGCTGGATCCCA
AAGGATAGGCAGGTGGATCATGTAGAACAGGGGAAAGGAGTTCCTGATC
GG

SG13S418

AACTAAAGAAAGCCACAAAAGTTCACCTCAATGCCAAGACATTTCT
TGATTTTTGAAAACCCAGTTGTGCGAACCACCCATCTATAGAACTTGAAA
GACTAAAACTATCTTACTCTAAACATTTTCTAGGAAGTTGATTCTACAAC
ACATTTTGGTTTTTCCAATTTGGCTTCTAATAATTATTTCAAAGTTTCTGTG[
A/G]CCTAAATTTTGTTTTACATTGATCCTTTGAATGGACTACTGTTTCCACA
TTTTAGAACATTTAAAAAGATATCTACAACCCGAGTCTAATCATAAAAAA
AATCAGACAGATCCAAAATGTGGAACATTCCACTAAAAAAGGAGTGGGG
AGAGGTCTTTATTCTTCCAAAAATATCAATGCCATAAAAGACAAAGACG

SG13S44

ACCCTTCAACCCCAGCCCAGCTGCTAACTGACTACAGCCACATGAA
CAGAACCAGGTGAGACCAGAGGAAACTTCCAGTCACCTACCAGATCATGA
CAAATAATAAACGATGTTTTTTAAACCACAAAGATTTGGAGCAGCATTG
TTACACAAAATTAGACAACCTATTACAGTTCGACTAAAAACATGTTTCAATTA
C[A/G]ATACTAAATTAGAAGTGTAAGAATGGGAGAAAAAATTCATACTTTA
AAAGTCATTTTTTCTCCTCCAAAAAATTCCTCAACTTTGAAAAAATGATTTTTAT
AATGCATAAAAAATTAAATAACCTTAGAATTTATATGAGTAGCATAGCCA
GCTGGCTTTATTATCTGTTGTACTCAACACTTCAATAATCACTGATGTTT

SG13S45

ATGACCTTACCTCGTTTTGTTTTCTTGTCTGAGAGAAACACATTAG
CAGTCTCCCATCTTGTTTTTCTTTCTGTCACCCAGGACAGAGGGCAGT
GGTGTGATCACAGCTCTGCAGCACGACTTCCCCAGGTTCAGGTGATCCTCC
CACCTCAGCCTCCCAAGGAGCTGGGACCACAGGCACATGCCACCACGTC[
C/G]AGCTTAATTTTGTATTTTTTTGGTAGAGATCAGGTTTTGCCTTATTGCC
CCAAGCTGATCTTGAATTCCTGGGCTGAAGCAATCTGCCTGCCCTGGCCTC
TCCAAGTGTTAGGATTACAGGTATAAGCCACCGTGCAGCCTTATATTTTGT
TTTAAATTTTCTCTGTATTTTTCTCTCTGGCAAATTGTTTAGGGA

FIG. 8.1

SG13S46

TTTTTTGGTAGAGATCAGGTTTTGCCTTATTGCCCAAGCTGATCTT
GAATTCCTGGGCTGAAGCAATCTGCCTGCCCTGGCCTCTCCAAGTGTTAGG
ATTACAGGTATAAGCCACCGTGCAGCCTTATATTTTGTTTTAAATTTTCCTC
TGTATTTTCTCTCTGGCAAATTGTTTAGGGAGTTTCTTTAGTTTATC[A/G]
GACTAAATTTCAAGGCTTTCCTTCCAATTTTGACATGTAAACAGTCCCTCA
TTTCTGCTTATCTAGTGATTATCCCAAATCTGTGTTTACAGTCTAGCTGTC
TCTCCTGAGATTAAGACTTGTTTCTCTAACTACCTGACGGCAGAATCTCCT
CTTGGAAGTATCAAGGAGGCAGTTCAAAACCTGAACTGGGCATT

SG13S50

GCTGATCTTGAATTCCTGGGCTGAAGCAATCTGCCTGCCCTGGCCT
CTCCAAGTGTTAGGATTACAGGTATAAGCCACCGTGCAGCCTTATATTTTG
TTTTAAATTTTCCTCTGTATTTTCTCTCTGGCAAATTGTTTAGGGAGTTTC
TTTAGTTTATCAGACTAAATTTCAAGGCTTTCCTTCCAATTTTGACATG[C/T]
JAAACAGTCCCTCATTTCTGCTTATCTAGTGATTATCCCAAATCTGTGTTT
ACAGTCTAGCTGTCTCTCCTGAGATTAAGACTTGTTTCTCTAACTACCTGA
CGGCAGAATCTCCTCTTGGAAGTATCAAGGAGGCAGTTCAAAACCTGAACT
GGGCATTGGCTCCACTCCTTCTCCTTCTCTTTACTATTAATACCC

SG13S52

TAAGTCTTATTTAGGCATCGTTTCTTCTGGGAGACCTTTGTAGAATC
TCTGAGGTTATGTTAACATGCTAAGGTTTTCTTGACATTCTCAGATTGGGT
TAGGTGAACTTTTAGCAACTTATCTTTTACTAAAAAGTCATCCCTCAGTA
TCTGTGGGGAATTGGTTCTAGGACTCCCTAAGGATATCAAAATCTGCAT[A/
G]AGCAGCCCAGGTGAGACCAGCAGAAGCACTTACAGTCACCTACAGGA
TCATGACAAATAATAAATCATGTTTAAAGCCACAAAGTCCTTTACATAAAA
TGGTATAGTATTTGCATATAACCTACACATCTTCCTGTATCCTTTAAATCAT
CTCTAGTTTATAATACCTCATACGATGAAAATACTACGTAAATAGTT

SG13S53

AAGCAGTTCCTAATTACTGGACATTCTCAGATCTGCTAGAGCTACA
TGTCCAATTACGAGAATATACTGGAAAAAGCCCTGGATTAGAAATGAGAG
GATGTAGGTTTTAGTACCAGGTCAGCCACCTTGTTAATGCAAATTTGAGTA
AATTGTTACTTCTTTTAGGCCCTTGTTTTTGCTGTTTTGTTTTCTGACAGT[A/
C]TGGTCTCTGTGGTCCAGGCTGGAGTGCAGAGGCACAATATCAGGTCCCT
GCAGTCTCTACCTCCCAGGATCAAGCCATTTTCATGCCTCATCCTCCTGAG
TAGCTGGGATTACAGGCATGTGCCACCACACCCTCGAACTCCTGACCTCA
AGTGATCTGCTTGCCTCAGCCTCCCAAAGTGCTGGGATTAGAGGTGT

SG13S55

GAATATACTGGAAAAAGCCCTGGATTAGAAATGAGAGGATGTAGG
TTTTAGTACCAGGTCAGCCACCTTGTTAATGCAAATTTGAGTAAATGTTA
CTTCTTTTAGGCCCTTGTTTTTGCTGTTTTGTTTTCTGACAGTATGGTCTCTG
TGGTCCAGGCTGGAGTGCAGAGGCACAATATCAGGTCCCTGCAGTCTCT[A/
G]CCTCCCAGGATCAAGCCATTTTCATGCCTCATCCTCCTGAGTAGCTGGG
ATTACAGGCATGTGCCACCACACCCTCGAACTCCTGACCTCAAGTGATCT
GCTTGCCTCAGCCTCCCAAAGTGCTGGGATTAGAGGTGTGAGCCACTGTG
CCTAGCCTTACACATTGTTTTCTTACTGGTAAAGTGGAATATCTAGA

SG13S56

GTTTTGTTTTTCTGACAGTATGGTCTCTGTGGTCCAGGCTGGAGTGC
AGAGGCACAATATCAGGTCCCTGCAGTCTCTACCTCCCAGGATCAAGCCA
TTTTCATGCCTCATCCTCCTGAGTAGCTGGGATTACAGGCATGTGCCACCA
CACCTCGAACTCCTGACCTCAAGTGATCTGCTTGCCTCAGCCTCCCAA[

FIG. 8.2

G/T]TGCTGGGATTAGAGGTGTGAGCCACTGTGCCTAGCCTTACACATTGTT
TTCTTACTGGTAAAGTGGGAATATCTAGAAGTTGCATGCTACATAAATTCA
ACCATATATTATTGGCAAAAAATTTTAAAGAAAAACATCAGCTTAAGAGT
ACTAATTGAGTACATGCCTTGGAATGAGCATGAGCTGGAAAGAACAAA
SG13S57

GGCAAAAAATTTTAAAGAAAAACATCAGCTTAAGAGTACTAATTG
AGTACATGCCTTGGAATGAGCATGAGCTGGAAAGAACAACCTGTTGTTA
CATCACTCATTGCTGTTTTTCATATGCTGCTCATTGTAAATCTTGCTCAGTGG
CATGATTTTAGTGTTTAAAGATTTATTTGTTTGTTTGGTTAGGACAAAGTC[
C/T]CTACACATAATCTACTTGCTTCATATATACATACTTATGCATATTATGT
ATGTACATACATGCTCTCAGGGCTCACATGAAAAAACAGCCATTCAGGTG
ATGTGATTTATCTCATATGCTTACTTTAGAGTCAACAGGGTGTGACTCCA
CTATACAATACTGGCATGGAGAACACATAAGTCAAAGTAGACAGGAC
SG13S58

TTTATTTGTTTGTTTGTTTAGGACAAAGTCTCTACACATAATCTACT
TGCTTCATATATACATACTTATGCATATTATGTATGTACATACATGCTCTC
AGGGCTCACATGAAAAAACAGCCATTCAGGTGATGTGATTTATCTCATAT
GCTTACTTTAGAGTCAACAGGGTGTGACTCCACTATACAATACTGGCAT[
A/G]GAGAACACATAAGTCAAAGTAGACAGGACCCAGCCGTACCATTGGCT
AGGGCACAAATATATTCACATATGTGGAGAATGATGTACGTAGAAAGGTC
TTCATTGCACAATGCTCTTTAATAAAGATCTGGAAAAAAAAAACCTAA
ATGTTCAAAGGATAGGGTAGATGAAATAATGGTACATTATAAAATGGAA
SG13S59

TCTGTCACCCAGGCTGGAGTGCAGTGGCATGATCATGTCTCCTTGC
AGCCTTGACTTCCCTGGCTCAGGTGGGCCTCCACCTCAGTCTCCCAAGTA
GCTGGAACACAGTCGTGCACCAACCATAGCCAGCTAAGATAGTGAGATGG
TGGCCCCACTGTCTTGCCCAGGCTGGACTCGATTTCTTGGGTGCAAGCACC
[C/G]TTCCCGCCTCAGCCTCCCAAAGTGCTGGGATTACAGGCATGAGTCAC
CATTCCAGCCTACTTGTCTTTAATTCTTAAAAATATTAATGTTGAGTTTTGT
CTCCCAGCATGTGGGAAAGATGTCATCCATTGCTTCTGTTTCTTGGAGGCC
TGGGAGCAAGGAGCCCAGGAACAGTATCACGAAGCTTGAGATAATAC
SG13S60

ATCATTGATGGGCATTTGGGTTGGTTCCAAGTCTTTGCTATTGTGAT
TTTTTTTTTTTTTTTTTTTTTTTTTAAAGACAGAGCCTCACTCTGTTGCCAGGC
TGGAGTGCGATGGCATGATCTCAGCTCACTGCAACCTCCGCCTCTCAGGTT
CAAGCAATTCTTCTGCCTCAGCCTCCCAAGTAGCTGGGACTACAGGC[A/G]
CCCACCACCAGGCCAGCTAATTTTTGTATTTTATAGTAGAGACAGGGTTTC
ACCATGTTGGTCAGGCTGGTCTTGAACCTCCAGACCTCATGATCTGCCTGCC
TTGGCCTCCCAAAGTGCTGAAATTACAGGTGTGAGCCACCATACCTGGCC
TAGGCAGTCTTTTTCAAACCTCTAAGACTGTGCTTGTGTCTCAGG
SG13S419

TGGTATGAGGTAAGGATCCATTTTTTTCCCATTTGCATAGCCAGTTT
TTGTAGCTCCACTTTATTTTCTCACTTGATCTGCCATGCCACCTCTAGCATG
TATCAACATATCATGTATGTGTGCAGCTGTTCCCTAACTCTCAATTTTATTC
TCTTGGTTACTTTGTCTAACCCAGCACTCATACTTTTTAAATTATTA[C/T]G
GCTACCTTGTAGGGCAAGAATCCTCACTTTTATTCAACTTCTTTGAAGTG
TCTTGATGCATATTTTTTCTGATCTTACTTGGCCATATATATTTTGGGGACA
GATGTGACATCATACCAAGCTTCTTTGCTTGACATTGTAGATATTTCTTA
TTCATTAATGTGCTAAAAATTTTGAGTTTGGTCATACAGTC

FIG. 8.3

SG13S61

GTTTCTAACATTATAGACACTAGTTTTAGGCTCTTGGAGGCTAGCA
GCAATTCTCAGAGGTAATGCAAGCTTCCCCATTTCTTCCCGTAGTCCTGTG
AAAGACCAGCCACCTCCAGAAGCCTACACATGAGTCTTCTCAGCCATACT
TTCTGCTTTTCCTAATGCCTCTCAGCAGCGTATTAGAAAGGCCATGATCGA
[C/T]GTACCTGTTACCTTCAGGCTTTGCATAAGGTGTATATGAAACATAAT
GAATTCGTGTTTAGGCTCAGGTCCCATCCCCAGGTTACCTCTTTATCTTG
GAGACACTTCTGGTCCCATAACATTTTCAGATAAGAGATATTCAACCTGTACC
CACCACGTAAGGAGAGGAATAGGTTTTAGAAAGAGGAGTCAGGGAGGCA

SG13S62

GCATCTATTAAAAGTGATGGTTTTAGTATCCTGTCTCATTTTTTTCCT
TTCCTTACATCATGTATTATAGGTAAACACATGCGCATGTGTGTATTTCCTC
TTTTAGACAAAGGATGAGATTACTACTGTTAGCTCAGTTTTTTTTTCCCTAC
TTAACATCTTTGCTTTTTATTTTTTAGACATATTTCTAAGACTATTAAA[C/T]A
TTAGACTTACGTAGCCCTTCTGTCAATTGTGAAATACATAGTTTACTAACAG
CTACCATCAAGATAAAGCCTTTATTTAAATAATTAACTTCTTAGTGGAAA
GCTAAGTAAGCACAGTTTATGGATTTTGGGAATTTTGCCTTGCATTTGTC
TGATATGGTAAAATATTGAGTTTGTTTTTCTCATAATGTTTAC

SG13S63

GATAACTCAATCCCCTTAAAGGGTTGTATCAAGCCATTGATAAGGG
CTCACTTTGATATAACCATTTTTCTGTTATTTAGACACTCTTTCACACTTCCT
ATTTTCCTCCTGGGGATGGTTTGAATGGATGACACAATACCATATTATAAA
AGCACTTTACAACTGTAACCTATGTTATAAATGTAATTATTACCTTAA[A/
G]GTTTTACCCTGTTTCAGATTTGAGTGGAAGTAGTTCTTTACAATACAAA
ACAACTTATTTTAACTTTTTTGCATTTCAAAGAATGATCAATCCACTTCA
GGTGCAGCATGGTTTCCAACCCTGACAGCATGGAAGAATCATTTATTTAG
CTTCTAAAAATGTGCAGGCTGTACCCTAGACCAGCCTTGGGGATTAG

SG13S64

TCCTCTCTCTCATTCTCTCTCTCTCTCTTTCTCTCTCTCCTTCTTTG
CTCCTTCATTCTCTCTCTCTCTCTTTTTTTTTTGAGACAGCATCTCACTAT
ATTGCCCAGGCTGTTCTCAAACCTCTGGGCTCAAGTGATCCTCCTGCCTCA
GCTTCTGAGTAGCTAGGACTACAGGCACATGCTATGGCAATACT[A/G]TT
TTAAACATTGTTTTCAAGGCTCCCCAGGTGATTCCAGTGTGGGTCATGTGG
TAGAGAACCACTGACACAGGCAAACAAAGGATACATAAAGTTGTCTATTT
AATGGGTAGGTGCAGGTAGTAGATAAGAGTGTAGCCACATAAACCACAT
GCTTAGTGAACGGTTTTGTTTTGTGTGTATGTGAGGGATTAGCAT

SG13S65

TTCAGGTTCCATTTAGCACGACAGCAGGGAAGGGACTGTTGGCAG
AAAAAACTGGGGCAGTGGGATTAAAGACAGACCACACATTCCAAAAGG
CACCGTGGGAGGGTCAGGGGGCGAGGTTAGGTCTAGGCTTCAGTGTCTG
GGAGACTCAGTCTTCACAGGGTGACAGCGATCAAGAGTGCAGCTTAGGCT
GGGT[A/G]CAGTGGCTCATGCCTGTAGTCCCAGCACTTTGGGAGGCCGAGA
CGGGAGGATTGCTTGAAGCCAGGAGTTTGAGACCAGTCTGACCAACATGG
CAAAACCCCATCTCTACTAAAAATACAAAAATCAACTGGGCATGGTGGCG
TGTGCCTGTAGTCCCAGCTACTTGAGAGGCTGAGGCAAGAGAATCACTTG
AACC

SG13S420

TAAATGATCATTATGTTTCATATTCACACATACAATAATGTACTCAA
GTTTATTGCTAAGGTAATTCAGAATCTCCTTATTTTGAAGTGTGCATTTGA
TATACCTGTTTGGGAATAACTAGTTTCTTATCTTTGACAGAAAATAATTTT

FIG. 8.4

GTTGTTTTGTTTTTACTAAAAAAGCATGGTGAAAAATGGCTCCATTTCTA[A
/T]GAGAGGTAACATAAATATCGCAATTTGCTGGGTGTCATTAAAGTAACT
CACAAGGGAAAAAATGCAAATTGGTATCTGCTGATGGAGTAAATCTCCGC
AGAAGTGATGACCCTGAAAGGATCAATATATTAAAGCCCCTCCCAGCTGG
TCATTCCAGATTGCAACAATAAAGCATTAAGTGTTAAACCTCAAGGCA
SG13S66

CTCATCAAGCCCACCTTTATACTTCATTTCTCCAGACTTCATGTCCA
GACTGTGGGATGAACAAGTGGTTATAAGGTTTTAGAGGCTCCTGTAGGAC
TAGATGGAAGGCAAAAAAAGGAAATAACCTTTAAGCATGCTCTCGATTCC
TTAAATCCCATCTGAAAGTCTTAAGGATGTCTTCTCAGTCATACTTATTTG[
A/G]CAATATTACCTAATTTTCTCCATTAGCCCAAGCTCAGGGGTCTTTCTT
CTTCCATATTCACATGGGTGCAATGGTTTTCTGAAAGGAAAAACAGCATT
CTAGGGCAGTAACATTTAATTAATCACAGGTACTTATCAAACCTACAAAAC
AGGCATTCCAGGAAGTGGGTGTTTCTGTTTGTAATAATTACACTCTCGTG
SG13S67

TAGGACTAGATGGAAGGCAAAAAAAGGAAATAACCTTTAAGCATG
CTCTCGATTCCCTTAAATCCCATCTGAAAGTCTTAAGGATGTCTTCTCAGTC
ATACTTATTTGACAATATTACCTAATTTTCTCCATTAGCCCAAGCTCAGGG
GTCTTTCTTCTTCCATATTCACATGGGTGCAATGGTTTTCTGAAAGGAAAA[
C/T]AGCATTACTAGGGCAGTAACATTTAATTAATCACAGGTACTTATCAAA
CTACAAAACAGGCATTCCAGGAAGTGGGTGTTTCTGTTTGTAATAATTACA
CTCTCGTGATCATGCTCCCACTAAATGTAAAGTTCGCTGAGGATGGAGGT
TTGGTCTCTTTGCTCTGTGCTGTAACCCCAACACTGCAGCAGGGCCTG
SG13S69

GCTGCATAGTCTCACTTAGGTGTGGAATCTAAAAAAGTCAAATTA
AAAAAATGTCAAGCAGAGAATAGAATGGTAGTTGCCAGGGACTCTGGG
AAGTAGCAGGGGTGGGGGTGGAGGGGAGGGGATGGGCAGAAGTTGGTCA
AAAGGTACAAAGTTTCAGGTAGACAGGTGTAAGTTCTGGGGATCTATTGT
ACAG[A/C]GTGGTGACTGTAGTTAATACTGTATTGTGTACTTAAAAATTGC
TCACCAAAAATGTTCTCACCAAAAAAATGATGTTTGGATATGTAAACAG
TTTGATTTAATCATTTTGACGTGTGTGTGTGTGTGTGTGTGTGTGTGTGT
GTATACATCAAAACATCACATTATATACCATATACAATTAATATATACAAT
T
SG13S70

GGGGTAAATGCTGACTGCCTGTTCTCTGGACAGGAATGGAGAAGA
TGGTGCTAGCAGGGTTGCTGTTTCATATGTAGACATTCATGCAGTCACTCTC
TTTTAGCACACTTCTTACTTCTGCCCTGGGTTCAGTTGCTGACTCTGAGCC
CAGAAACCTTCTAGGGTTCTGTTAGGTAGATTGGCTTCCACCGTCTTTGC[
A/G]ACAACCACAGAAAATTCTAGACTGTTTTCTCTTCGGGGCTTCATTAGTC
AACTTGCTTCAGTCTGTCTTGCATCTTCTAAATATTTATAGATCTCTCTCTT
TTGTTGGAGTGGCAGAAAATGCTAGTTGACCACCCAATATTCAAATTATC
CTGCCTCCTTAATAACAGAATATCATTGGATGTGGTGGGTAAATAAT
SG13S71

ATGGAGAAGATGGTGCTAGCAGGGTTGCTGTTTCATATGTAGACATT
CATGCAGTCACTCTCTTTTCAGCACACTTCTTACTTCTGCCCTGGGTTCAGT
TGCTGACTCTGAGCCCAGAAACCTTCTAGGGTTCTGTTAGGTAGATTGGCT
TCCACCGTCTTTGCGACAACCACAGAAAATTCTAGACTGTTTTCTCTTC[A/
G]GGCTTCATTAGTCAACTTGCTTCAGTCTGTCTTGCATCTTCTAAATATTT
ATAGATCTCTCTCTTTTGTGGAGTGGCAGAAAATGCTAGTTGACCACCCA

FIG. 8.5

ATATTCAAATTATCCTGCCTCCTTAATAACAGAATATCATTGGATGTGGTG
GGTAAATAATATACCCTAACTTTCCTTGCAGAGAGGGGTGGCCAA
SG13S72

CAGGGTTGCTGTTTCATATGTAGACATTCATGCAGTCACTCTCTTTTC
AGCACACTTCTTACTTCTGCCCTGGGTTCAGTTGCTGACTCTGAGCCCAGA
AACCTTCTAGGGTTCTGTTAGGTAGATTGGCTTCCACCGTCTTTGCGACAA
CCACAGAAAATTCTAGACTGTTTTCTCTTCGGGCTTCATTAGTCAACTT[G/
T]CTTCAGTCTGTCTTGCATCTTCTAAATATTTATAGATCTCTCTCTTTTGT
GGAGTGGCAGAAAATGCTAGTTGACCACCCAATATTCAAATTATCCTGCC
TCCTTAATAACAGAATATCATTGGATGTGGTGGGTAAATAATATACCCTA
ACTTTCCTTGCAGAGAGGGGTGGCCAATGAGATGGAAATGAAAGTC
SG13S73

TGGGATTGAGTTCTTGATTTGATTTTGAAGCTTGGCCATCATTGGTGT
ATAGCAGTGCTAGTGATTTGTGTACATTGATTTTGTAACCTAACACTACTA
AATTCATTATCAAATCTGGGAGATTTTGGAGATTCTTAGGATTTTCTA
GGTATGAGATCATATCATTGGTAGAGGTAGTTTGAAGTTTCTCTTTTCCA[A/
G]TTTGGATGCCCTTTATTTCTTTCTTGCCTGATTGCTCTGACTAGGGCTT
CTAGTACTATGTTGAATAGAAATGGTGAAAAGTGGGCATCCTTGTCTCATT
CTAATTTTTAGGGGGAAATGCTTTCAACTTTTCCCCATTCAATTTGATGTTG
GCTGTGAGTTTGTTCATAGATGATTCTTACTATTTTGAGATATA
SG13S99

TCTTTTGCCCTGCCTTTCTGCCTTTCTGTCTTTTAATTTGCGGGCTT
TTGGCAACCACAGCACGGGTCTGGTTTCTTAGGAGTTTCTTTGTAGGATC
AAACCGCTAGTTGGCTCTTGGCCCTGTGATAGGGCCCTGGGCTAACTTATT
GGGAAAATGTTGCTGTAACCCCTGCCCAGAGGTGCCTGTGACATGGGC[C/
T]GCCATCTTCTCCTCTTCCCTTGGCTTCAGCCCCACCTAGAAACCTGAACA
AACATTTTCCTTGACATTTCATAAAGTGTGAGTGGCTCCTCATTTAGCAAA
ATACATCCCAGGGAAGTTCAAAAGTGAAAAAAGGCCGTAACCTTCTTCTC
TTCTCAGGGACCTACAGAAAATATGTGGCACCTCGGCAGCCTGGCC
SG13S382

CATGGATTTTGTTTTCCAAGTGGCAAGATGGCGCCTCCACCTTTGGT
ATCCTATTTTAGTTCTTGGCAGAAAGAAAGGAACAGGCTAATGGCCCTGA
TGAGTCTACCCCTTTTAACAGGAGAAAATTTAAAAAACAAAAACCATGA
AACCCTTTCCCAGAGGCAACAACCAGAATTCCATTTATCTTTCATTGACCA
[A/G]AACAGACCACATGGTCACTGGTGGTGGCAATGGAGACTGGGGAGAT
GAATATTTTAAAGGTGGCATATTCCAGAAGAACACTGTGCACTGATTGCAT
TAATGAACCCATTAATGTGCCAAGGGGAGGTTTACCTATGAGCATGGGCA
AATTAGAACCCACTCTTGGAGCTGCAGGTGAGCCAATCCCACCTAAACAG
SG13S383

TGGTGGTGGCAATGGAGACTGGGGAGATGAATATTTTAAAGGTGGC
ATATTCCAGAAGAACTGTGCACTGATTGCATTAATGAACCCATTAATG
TGCCAAGGGGAGGTTTACCTATGAGCATGGGCAAATTAGAACCCACTCTT
GGAGCTGCAGGTGAGCCAATCCCACCTAAACAGTGTGGATGCTACAAGAT
GG[A/G]GAAGTAAATTGATTCTATTCCATACCCTAACCTCTCTCCAAGATG
TATTCTTAAATAGAAAGAGGGAAGACAGAAGAAAACATCCAGAATATATT
TTTATTGTCTTTTACTTCTTCAGTGCATTTTAGATCAGTGCTTCTCAATCTG
GCAAGGGGCATGCAGGAGGATGTGAGTTTTATCAGGAAACTACACAAC
C

SG13S384

TGAGCCAATCCCACCTAAACAGTGTGGATGCTACAAGATGGGGAA

FIG. 8.6

GTAAATTGATTCTATTCCATACCCTAACCTCTCTCCAAGATGTATTCTTAA
AATAGAAGAGGGAAGACAGAAGAAAACATCCAGAATATATTTTTATTGTC
TTTTACTTCTTCAGTGCATTTTAGATCAGTGCTTCTCAATCTGGCAAGGGG
C[A/G]TGCAGGAGGATGTGAGTTTTATCAGGAAAACCTACACAACCCCCCA
ACCACAATGCTACCCCCACTCCTGTGGACCTTCTTTAAGAGAGACTCACTA
TTATAGATGGAGTTGATACGATTTTAAGAGAGGCCATATATTATTGCTTT
CTGTCTTGAAAACTTGTGATTTTCTGTATTGTGCTACTGCCAAAGAGA
SG13S381

GGGTTGCAGTGAGCAGAGATCACACCATTGCACTCCAGCCTGGGTG
GCAGAGCGAGATTCTGTCTAAAAACAACACCGTATTTGGGGCATGCTGA
TACTAAAAAATTATTCAATTGTTTGTCTGAAATTAAATTTAAATTGGGGGC
CCTGTATTTTACTGGGCAACCCATTTGCAATATCAGCAACAATCTCTTATT[
C/G]AGACCACTGATTAAGTGTGCAAAATTTGAATCTCTGAACAGTACCTA
TGTCTTGATATCTTAAATTAATGAGTGTCTTAGACACTCAAAGCAGGAGG
AAGCATTATGGCAGATGTTTGAGCCCCAGAGATGTCCATGAGCACAGCAT
AGAGCTCAGAGCCTTCTTTATTATTGCTTCACGACAGAGCAAAGGACT
SG13S366

CATTTGCAATATCAGCAACAATCTCTTATTCAGACCACTGATTAAG
TGTGCAAAATTTGAATCTCTGAACAGTACCTATGTCCTTGATATCTTAAAT
TAATGAGTGTCTTAGACACTCAAAGCAGGAGGAAGCATTATGGCAGATGT
TTGAGCCCCAGAGATGTCCATGAGCACAGCATAGAGCTCAGAGCCTTCTT
T[A/G]TTATTTGCTTCACGACAGAGCAAAGGACTGCAGCAGGTTGACTGAT
ATAAAAGTTTTACCATGTCTCACAGCAGGCCTTTGCTCAAGTTTCCAGTAA
GGATATTGTATCATTCTTGCCCTGCAGTACTTGTAATCCACTTACACTGC
CTGCTGTTGAGTCATTTGTTTCGTCTTGAGTAGCATGTCATCCTTGTTT
SG13S385

TTGCAGTTCTCATTGCTGGGGAGTCTAAACTGGAATAAAACACCCA
CTATCTCCATCAGGCTTGCACTAGAGCCCAGCTCTAGCTGGAGAGAAAGA
AGCTAACCCGCACAGACACAGGACTGTAGGCAGGGAGCATCCGGGGGTA
TTTGGGTCTGCTGCTGATGTGCCTAAGGCCAACTTCTCTCTGGCCATGCT
GG[C/T]GTGCATGAGCTCACTAATCTTCCTTTTTGCCTTCCATTTTCTCAA
TCCTGACTTAGCAAAGGTTGGGCAAAAGAGACTCTGTGTGAGTTCGAGCA
AAGCCTGAGATGCTGGATTTTCCAAGATACGAGAAGGGGCTGGGGGCTGG
GTGAACTGGTGGTGGAGGAGGGAAGGATTAATTTCCCAAGGAGGGGAAG
GG
SG13S386

GAGAAAGAAGCTAACCCGCACAGACACAGGACTGTAGGCAGGGA
GCATCCGGGGGTATTTGGGTCTGCTGATGTGCCTAAGGCCAACTTCT
CTCTGGCCATGCTGGCGTGCATGAGCTCACTAATCTTCCTTTTGCCTTCC
ATTTTCTCCAATCCTGACTTAGCAAAGGTTGGGCAAAAGAGACTCTGTGT
GA[A/G]TTCGAGCAAAGCCTGAGATGCTGGATTTTCCAAGATACGAGAAG
GGGCTGGGGGCTGGGTGAACTGGTGGTGGAGGAGGGAAGGATTAATTTCC
CAAGGAGGGGAAGGGGCCAGGACATCAGGCCCCGGGGACTTTGAAGAGA
GGGTCGTGGGTAGGAGGTAGATCAAGTGGAGTGACACAAAGGTCAGGAA
AGAGG
SG13S1

CATGCCTCCTACAAATTTGACCTGGGCCCAGGGCCATGTTCCGGTGG
TTTTTAAGAACCGAGGCTCCCAGAAGCAGTATTGGGCAGCTAGAGTGGCC
CCAGGATCTATATCAAACCTCTACCTGTTTCTGAACCAAATTTCTTCTAGAA
TTTTATTCCATAAATCTGAATTATGGTGTGAGACTCCTAGCATACACTAAA[

FIG. 8.7

G/T]GAACTCTCTGCCTTGCATTAAATAACAGGAGTTACCCCTGGAGGTAA
CTCCTAGCCCTGGCTCTTTAGAGAACAGATGCCGAATAGGCATTAGGGGA
TGTGATGGATGTGCTAACTTTCAAAAAAAAAAAAAAAAAAAGGCCTGAG
CTGAGTGCTCAGAGATTCACAAAAAGCTGACAGCATCTCTCTGTTCCATTG
SG13S2

CTTTGGAGCCTGGCAGCCTGGCTTTGAGAACCGGGCTTTAACTTGT
CACATGACTATGGCCAAGTTCCTGGGGCTCTCCAAGCTTCACTTCCTCTGT
AAAAAGGGCAATAATATAATACCTGTCTTATTGGGTTTTGTCCATGTTAGA
TGAGACATTGGGTACAAAGCACTTGGTCCCGTGCCTGGCACATTTACTGC[
A/G]CTTAATGTATGATAGTTTTCTTATTATTCTAATAAACAATATGGCTTTG
GGAGTATAGTTCTGCCACATTGCAGTGGCCAGAGTGAAGGTGGTGAGTGC
CTTCTGGGGCCCTGGGAGTCAAGGTTATCCGCATGCCCTTTCTTGCTTGCT
CCTCAGTGTGGCTGCCTCTATGTCCACACCATGCAGATGCAACAGGT
SG13S367

ACATGATCATCCCCCTTGGGCTTCTGGTTTTTTTTCTTTCAGGACCTT
ATTTTCAGGCAAGTGGCCTTTGACCTCTAAGGCTGTCCTTTCCTAGCTACC
GAATCCAGCATTCAAAGTGATGGAAATATGTATATATAGTAATAGTAAAA
TATCAGCACTTAATGGCCTGATAAGAATGTCACTGCAATGCTGAGTTTGG[
A/G]CCAACATTTGCCTGCTCCTGCCATTGAGCCCGGGCTCCCCTCCAGAGC
TGAGCTGCTGCAAGGGATCTGAGTAACTAGGGCTGTGTCAGAGTGGCGAT
GACAGCCACCACATGCTAAGGAAGAGATCCCCAAGGACAAGGAGAATCC
CACGTGGAGCTACTTGCTTCTTTGTCACTTGTTTTTCTTATTTACAA
SG13S388

CCGAATCCAGCATTCAAAGTGATGGAAATATGTATATATAGTAATA
GTAAATATCAGCACTTAATGGCCTGATAAGAATGTCACTGCAATGCTGA
GTTTGGACCAACATTTGCCTGCTCCTGCCATTGAGCCCGGGCTCCCCTCCA
GAGCTGAGCTGCTGCAAGGGATCTGAGTAACTAGGGCTGTGTCAGAGTGG
C[A/G]ATGACAGCCACCACATGCTAAGGAAGAGATCCCCAAGGACAAGGA
GAATCCCACGTGGAGCTACTTGCTTCTTTGTCACTTGTTTTTCTTATTTT
ACAACCTTCTAAAACACAATCTCTCAACCTCTATTGTTAGCTTGCATTTTT
CAATCATGAGCACAGCTTTACCTGGCTCCATGCTTTGATTGACTCTACC
SG13S10

TCTTATTTACAAACCTTCTAAAACACAATCTCTCAACCTCTATTGTT
AGCTTGCATTTTTCAATCATGAGCACAGCTTTACCTGGCTCCATGCTTTGA
TTGACTCTACCTGCCAACACTGCAACAACAGGGAAAGGGACACCGGCCTC
ATACCATTAGATGGTGTGTAGCCTGGGCATGAGGATAATTA AAAA ACTCCC[
A/T]AGGGGATTTTAAACATGTAACACAGTTTGGAAACCATTGATGTAAGAT
CTTCTTACTCAACATGTGCTCCAAGGAGCTGTTGTATCAGCTTATCAGAAA
TGTAGATCAGGCCGCACTTGGACCTGTAGAATCAGAATCTGCATTTTATCA
GATTCCGACATTATTTGTATGAACATTAGCTTTTGAGAAGTGTTGCTT
SG13S3

CTTTTGACACCAACTACAAGTCAAGGGGTTCCCCAAACCACCCTGA
GTTGTGATAATTGCTGGGAGATCTGACAGAACTCACTGAAGGTTGTTAT
ACTCATGGTTGTGATCTCTTATAGGGAGGGAATACAGATTAAAATCAGCC
AAAGGAAGAAGCACACAGCACAGAGTCCAGGACAGTGCCTGACATGGAG
CCC[C/T]TACGGTCTCTCCCGTGGAGTCACGGACAGCGCCACTCTCCTGG
CATTGATGTGTGACAACACACAGGGAGTGTTCCCCACCAGGGAAGCCTTG
GTGTCCAGGGTCTTTACTGTGGCTCTGTACATGAGCACAGCTGACTGCCC
ATGCGGCCGATCTGTTCCCAGACTCTCCACCGCTACACATCACTCACAGTC
C

FIG. 8.8

SG13S368

GTGGCTCACAGAACTCAGGGAAACACAGCTACCAGTTTATTGCGA
AGGACATTTTAAAGGATAAAAGTAGGCAGATAAAGAGATGCATAGGGCG
AGGTGTGGAAGGTCCCTAGTGCAGGAGCTTCTGTCCATGTGGAGCGGGG
GTGCACCACCTCTCAGTACATGAATGAGTTCTCCTTCACCTGCCTATCAG
CCT[C/T]TACATGTTTCACTCCCCAACCCAGTCCTCTTGGGTTTTTATGGAA
GCTTCAAGACACCCACATTCTTTCCCCAGAGTATAGGGCAAGACCTTCTCT
GGGGAGGGTTTTAAGACCCACAGTCAGAAAGGTGGGGTGGGGTCAAGAT
TAGAGTCCTGCCTTGACGGGCAGGTGAAAGGGGTAGGGGGAGTAGGTGA
GAA

SG13S369

CGGGGGTGCACCACCCTCTCAGTACATGAATGAGTTCTCCTTCACC
TGCCTATCAGCCTCTACATGTTTCACTCCCCAACCCAGTCCTCTTGGGTTT
TTATGGAAGCTTCAAGACACCCACATTCTTTCCCCAGAGTATAGGGCAAG
ACCTTCTCTGGGGAGGGTTTTAAGACCCACAGTCAGAAAGGTGGGGTGGG
G[G/T]CAAGATTAGAGTCCTGCCTTGACGGGCAGGTGAAAGGGGTAGGGG
GAGTAGGTGAGAAAAATTCTGTTTATTTTTTCTTTTTTTTTTGAGACGGAG
TTTCACTCTTGTTGCCAGGGTGGAGTGCAATGGCACAATCTCAGCTCACT
GCAACCTCCGCCTCCCAGGTTTAAGCGATTCTCCTGCCTCAGCCTCCCC

SG13S370

ATGAGTTCTCCTTCACCTGCCTATCAGCCTCTACATGTTTCACTCCC
CAACCCAGTCCTCTTGGGTTTTTATGGAAGCTTCAAGACACCCACATTCTT
TCCCCAGAGTATAGGGCAAGACCTTCTCTGGGGAGGGTTTTAAGACCCAC
AGTCAGAAAGGTGGGGTGGGGTCAAGATTAGAGTCCTGCCTTGACGGGCA
[A/G]GTGAAAGGGGTAGGGGGAGTAGGTGAGAAAAATTCTGTTTATTTTTT
CTTTTTTTTTTGAGACGGAGTTTCACTCTTGTTGCCAGGGTGGAGTGCA
ATGGCACAATCTCAGCTCACTGCAACCTCCGCCTCCCAGGTTTAAGCGATT
CTCCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCGTGTGCCACC

SG13S4

TCTTCATTCCACAAAGCTCAGTGTCAAAACATGGGGTTTACACTGG
AAGCTGAGGTCACATCAGTAGCCGGGATCAGGGTCGCCCTAGCTGCCCAA
TGCAGCTCCCAGGCCTCCTGTAAAACCTTGACCTTTGAGGTCATGACAGCC
CTCTCCTGCTATGCTCATAGCTGACCACTGAACTCCTGGACACTCCCTCCC[
G/C]CAAGTTCACAGAGAATGTGGGCACATGCCTTACAGTCTTCCCTTGATC
CAAATACTGCCTTCATCTTGAGTGACAGCAGCATCTTTTGGATGTCTTGG
CCTGTCTAGCTTTATTTTTTTGTGTTCTGCCATCAAGTTGCTACTTCTGTTG
CCATCGTGCCTGTCAGCGCAGTGCAGGCTGTGGTGAAATCCCACGA

SG13S5

TATTTTTTTGTGTTCTGCCATCAAGTTGCTACTTCTGTTGCCATCGTG
CCTGTCAGCGCAGTGCAGGCTGTGGTGAAATCCCACGAACTCAGGCATCA
CACTGACCGGGTCTGAGTCCTGTCTCAGTTGTCAGCTAGTTGTGCAATGAA
GGGAAAGGGACCTACACTTTCCAAGCCTCAATCACTCATCTATGGCAT[G
/T]GTGACAATAATGGAGGTTGATTTAAAGTCCTTTGTAAGAATTAAGAGTT
ATAATAGACATAAAGTGCTGTATCTGGTATACCTAGAAAACATTCCATAA
AAGTTAGTAATTGTTGGTCATGTAATGATGACTCTCTAGGCTAGGATTTC
GCTTCATTGCATGCACATGGTGCACCTCACAGGGCGTGACCTCTCTCT

SG13S389

GGTATACCTAGAAAACATTCCATAAAAGTTAGTAATTGTTGGTCAT
GTAATGATGACTCTCTAGGCTAGGATTTCACTTCATTGCATGCACATGGT
GCACTCACAGGGCGTGACCTCTCTGTCTCAGTAACCTCATCTGAGGACC

FIG. 8.9

GGGATAATCATACCGCTTCAAAGGGATGTCATAAAGATTAAATAATATGT[
A/G]TAAGGCTGCTTGCATTTAGCTGCATTCAACAAATATTTCTGTATCTTT
CTCCTCATTTCTCCTTACTTTCTTGCTTATTATCTGCTCTAGGTATAGATTTC
AGAGAACTAAGCTTGTTACAATCCTTCATAAAATAACCAGGTTGGTTAGG
GCATTTCCAAGAGTCAATACTGTTTAGTGACTATTCTCTGTTTAAT
SG13S90

AAGGCTGCTTGCATTTAGCTGCATTCAACAAATATTTCTGTATCTTT
CTCCTCATTTCTCCTTACTTTCTTGCTTATTATCTGCTCTAGGTATAGATTTC
AGAGAACTAAGCTTGTTACAATCCTTCATAAAATAACCAGGTTGGTTAGG
GCATTTCCAAGAGTCAATACTGTTTAGTGACTATTCTCTGTTTAATCT[A/C]
TTTTGATTGTCCAGGGTCATCTTTTGCTATGTCATAGGTTGTTGGCTTCTTC
TAGAGAAGTGAGACGATGGACAAGTTCCAAGTGAGTGAGGCGACTGGTC
AGGATATTCCGCTGAAAACTCATGTCAGTTCTAATTCGTGATTGTAATTC
AATCACAGCCTGAGAACAGTAGGACTGTAGTTCAAATGCTCTGTT
SG13S390

CCTGGGTTCAAGCAATTCTCCTGCCTCAGCCTCCCAAGTAGCTGGG
ACTACAGGCACATGCCACCACGCCCAGATAATTTTCGTATTTTATAGTAGAG
ACGGGGTTTCCCCTTGTTGGCCAGGGTGGTCTTGATCTCTTGACCTCATGA
TCCGCCCACCTCGGCCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCACC[
A/G]CGCCCGGCCTCTAGAGGATAATTTTAAATGTGCTTTTGCATTTGGAA
AATGTGATTGGCATTTTTTTCTAATTTTCTAATATGATACGCTGTCGGATGC
TATGGATTACTTAAACCCTCTGGCTACCTAGAAAGATCTTTAAGTGGTTCT
CAACAAGCTTCATACGCAATGTAAATTGTATTATCTCTCAGGATGT
SG13S6

TGTGATTGGCATTTTTTTCTAATTTTCTAATATGATACGCTGTCGGA
TGCTATGGATTACTTAAACCCTCTGGCTACCTAGAAAGATCTTTAAGTGGT
TCTCAACAAGCTTCATACGCAATGTAAATTGTATTATCTCTCAGGATGTGT
GAGAACATCTGTTTTTCTTCTAATGCAGTAAACATATAAGGGTCTCTTG[A/
G]GATATCTTTTAAATAGACTTAATACAACATTCAGGAATGATAACAAAAT
ATAATCACAGTTGTAAGGGAATGTGAGCATTTCATATTAATAACATTGGA
ACCTTATGTTTAATACAGTGTTAAAAGTTGACAAACATGTAGGAGTCAGA
AAATTCAATTAAATTATCACAGTAATATGAATTTAGCCACATCCTGT
SG13S391

ACTTAAACCCTCTGGCTACCTAGAAAGATCTTTAAGTGGTTCTCAA
CAAGCTTCATACGCAATGTAAATTGTATTATCTCTCAGGATGTGTGAGAAC
ATCTGTTTTTCTTCTAATGCAGTAAACATATAAGGGTCTCTTGGGATATCT
TTTAAATAGACTTAATACAACATTCAGGAATGATAACAAAATATAATCAC[
A/G]GTTGTAAGGGAATGTGAGCATTTCATATTAATAACATTGGAACCTTAT
GTTAATACAGTGTTAAAAGTTGACAAACATGTAGGAGTCAGAAAATTCA
ATTAAAATTATCACAGTAATATGAATTTAGCCACATCCTGTGTTAGTTATG
AAATCCATTTAACACCACAAACAGTAATATTTTTAGCCAGTTTATTCA
SG13S392

CATTTAACACCACAAACAGTAATATTTTTAGCCAGTTTATTCAAAA
GGAAAACAGGAACTAAACCACTTTCATGCAATATATACTCTGTTAATGTG
GTCAGGCTAATTTTGCTGGGGGAAGGAACTTAACTTTGAATATTTGAATG
CCCAGTCATTTAATCTGAATATCCTATTTCTTGCTGTTGCAAAAATTTTT[
G/T]TCAATAAAAGGCAGAAAAAGAAATCTCTTCTCCATGCTCATCCCTAA
GAGAATGGGTGTCTGTACCCTGAGAGCATTATGAGAGGGGACAACCAC
TTTTCTAATTTTCTTCCCACTTCTCTGTGGGCACAAATGCTCTTTGGTTGA
AAGAGTTGTAATTCAGTCCCAAGATGAGGTGTGGTTACTGCATCCCTA

FIG. 8.10

SG13S371

TCAATCCATGCTCCACACTGCAGCCAGAGTGCTCTACAATGCAAAT
CCATTTGTGAGACTCCTCCTCTTAAATCCTCAAGTGGCTTCTCTTTGCCCC
CAGGATCATTTTGAAACTCCTTAATGGAAGAGGCATGGCCCTTTGGGATG
TGGTTCCCCAACCCCTCCCACATCATCTTTCAATCAGATTTCCTACTAA[A
/G]TGGAAATTTTTTCAGGTCCTCAACTTTATGGTGACTTTCTCTTGCTCAGG
ATCTTTGAACATACTGTTTCTTCTTCTCTTTGTATTTGCCAAGACAACACT
TCCTCTGGTAAGATTTTCTGACATCCTCTATAAAAAAAGATTGAGATAGT
TGACTACCCAAAATGTTTCCCATTCATTCCAAGCTCTATTCAAG

SG13S372

AACACTTCCTCTGGTAAGATTTTCTGACATCCTCTATAAAAAAAG
ATTGAGATAGTTGACTACCCAAAATGTTTCCCATTCATTCCAAGCTCTATT
CAAGGCAGTAAAGTGCCCGGCTGACAGATTGCATTCTCTCATCTTTTCTGAA
GCTAGCAATGGCCATGCAACAGCATTCTGGCCAATAAGATAGAAGTCGAA
[A/G]TTGAAGGGTGGGATTTCCAAGAAAGCTCGTTGAAGACATAATTCCTC
ATTTCACTTCTTACTCTTTCTCTTCTCTTCTGCTTCTTAAATGCGGTGCAGATG
GCAGACACTTCAAAGCTGTCTCAGGCAATCAGGTGATGTTAAGGCAGAAA
CCAGCTTTATGATGGGTAGAACAGGAAGAAAGAAGGCACCTATGTTCT

SG13S393

CCTACAAATCTCATGTTGACATTTTATCCCTAATATTGGAGGCAGG
GCCTAGTAGGAGGTGTTTTGGTCATAGTGATAAATGGCTTGGTGCCGTTCT
CACAGTAACGAGTGAGTTTTTATTCTAGTGGTTCCTGCAAGAACTGATTGT
TAAAGAGCTTGGATCCTTCCACCCCTCTCTCACTCTTGCTTCTCTCTC[A/
T]CACCTTGTAATCTCTACAAGCTCTTCACCTCCCTTCTCCTTTTGCCATA
AGTGGAAGATTTCTGAGGCCTCACCAGAAGCAGATGTTGGTTCCATGCTT
CTTGACAGCCTGCAGAACCATGAGCCAAATCAACTTCTTTTCTTTATAAT
TATCCAGTCTCAGGTATTCTTTATAGCAACACAAATGGACTAAGA

SG13S373

GTTGTTTTCCAGCTTTGAACTATTTTGAATCCTAAAAGACTGCCAGTT
TTGAATGAGACCCCAAGACAATGAATGTAGGCTCTGTATACAAGTTCAGG
CTGCTGGGCAACTTAGGCCTTAAGACACAACCTCTGCCACTTAGGCCTTAA
GACACAACCTGACATGATGGTGCTTAAAGTGGCTGTGATGGAAAAGGAGG
CT[A/G]TTTGGAGCCTTTGGAGTGCTTTTATAGGTGAACCCAGCATAGCA
CCTAATGATTTGGAGCAAAGCTGTGTCATTCCCCAAAGATAACTATTCGCC
TTTTGAGAAACATCTTCTAGCTACTATCAATAATAAACACAGAATGCATC
ACCATGGGCCACCGTGTGTCTTTTGACCTGAGTTTCCATTGTGAACAAGA

SG13S374

AACTCTGCCACTTAGGCCTTAAGACACAACCTGACATGATGGTGCTT
AAAGTGGCTGTGATGGAAAAGGAGGCTGTTTGGAGCCTTTGGAGTGCCTT
TATAGGTGAACCCCAAGCATAGCACCTAATGATTTGGAGCAAAGCTGTGTC
ATTCCCCAAAGATAACTATTCGCCTTTTGAGAAACATCTTCTAGCTACTAT
C[A/G]ATAATAAACACAGAATGCATCACCATGGGCCACCGTGTGTCTTTT
GACCTGAGTTTCCATTGTGAACAAGAGTCATTTGATCCAAGGCAGAAAGT
TGGGTGCACACAGCAGTGTTCATCATCAAATGGAATATGAGATTGGGCC
CAAGTAGGTCCTGCAGACACAAATAAGTTGCAAGAGCAAGTAGTACAGG
CG

SG13S375

GAAAAGGAGGCTGTTTGGAGCCTTTGGAGTGCCTTTATAGGTGAAC
CCCAGCATAGCACCTAATGATTTGGAGCAAAGCTGTGTCATTCCCCAAG
ATAACTATTCGCCTTTTGAGAAACATCTTCTAGCTACTATCAATAATAAAC

FIG. 8.11

ACAGAATGCATCACCATGGGCCACCGTGTTGTCTTTTGACCTGAGTTTCCA
[C/T]TGTGAACAAGAGTCATTTGATCCAAGGCAGAAAGTTGGGTGCACAC
AGCAGTGTTCATCATCAAATGGAATATGAGATTGGGCCCAAGTAGGTCC
TGCAGACACAAATAAGTTGCAAGAGCAAGTAGTACAGGCGCTTGGCCTGG
CCAGTACTGTTGCCAAGTTGACTGCTTCCCCTCAGTCTGCATCTGTGGCTT
SG13S376

CCCCAAAGATAACTATTCGCCTTTTGAGAAACATCTTCTAGCTACT
ATCAATAATAAACACAGAATGCATCACCATGGGCCACCGTGTTGTCTTTT
GACCTGAGTTTCCATTGTGAACAAGAGTCATTTGATCCAAGGCAGAAAGT
TGGGTGCACACAGCAGTGTTCATCATCAAATGGAATATGAGATTGGGCC
CA[A/G]GTAGGTCCTGCAGACACAAATAAGTTGCAAGAGCAAGTAGTACA
GGCGCTTGGCCTGGCCAGTACTGTTGCCAAGTTGACTGCTTCCCCTCAGTC
TGCATCTGTGGCTTCATGGGGAGTTTCTATGACCACTTGATGGAGGAAA
AAACAAATTGGAGCATAGTTTATAGTGCTGGTACTACCCAAAGTGGCTAG
CT
SG13S394

GTCCGTGAGTTACAGATCTACACAAAATCACAGAGAGTGGTTAATC
GTTTAGTCTGATGGTCAGGGACTTCCAAGAGACATGATTAGAAAACCTGGT
GACAAGGAGTCCTGGGGAAGAGGCATATGGATACCTCTGAACACACACA
AAACATGAGAATATGTATCCCATATGAATGTTAACCAAAGAGCAGCCACA
ACA[C/G]AAGAGGATTTTAAAATCAGCTGAATAAGATGATTCTTGACA
GCATCAGCTAGTCTCTTTCCCCAGCCACTGTTGCCCAGTGGGCTTACATAT
ATCATGGCCATGGGGGCAGGGCTATGTATGGACACAGCAACATGAATTTT
CACTCATCAAGGCCAATTTGGCTCCAGCCATTGCTGAGTGCTCAGCCTGCC
A

SG13S25

ACATGATTAGAAAACCTGGTGACAAGGAGTCCTGGGGAAGAGGCAT
ATGGATACCTCTGAACACACACAAAACATGAGAATATGTATCCCATATGA
ATGTTAACCAAAGAGCAGCCACAACAGAAGAGGATTTTAAAATCAGCTG
AATAAGATGATTCTTCTGACAGCATCAGCTAGTCTCTTTCCCCAGCCACT
GTT[A/G]CCCAGTGGGCTTACATATATCATGGCCATGGGGGCAGGGCTATG
TATGGACACAGCAACATGAATTTCCACTCATCAAGGCCAATTTGGCTCCA
GCCATTGCTGAGTGCTCAGCCTGCCAAGATAGAAATCTACGCCAATATGG
CACCATTCCCTGGGCTAGAAAACCAACTGGTGGAAGGTTGATTACATTGG
ACC

SG13S395

GGGAATACAATGGTGGTTCCTAACTGACAGCTGAGTTTGCCAT
CTCCTCGTGCCAGTGAATACACAAGCAAGGAAGGGGGTTCCTTTCTCACC
TAGGGTGACTGATCCTAATTACCAAGGAGAAATTGGACTGCCACTTCACA
ATGAGGGTGAGGAGTATGTACTCTATGTGTCTGTGATTAATGTCAATAGA
AA[A/G]TGACACCAACCTAGTACACAGAGGACTGATCATGGTCCAGGCCC
TTCAGGAATGAAGATTTGAGTCACCAGGCAAGGAACCTGGACTCACTGAG
GAGGGCATATTCCAAGGAGAATATTTTATCTATGTCCATCTATGTCCATCT
ATATTCCATCTGTGTTCCCCTTGGAATTCCTATTCATGAACATGGGGAATT
C

SG13S396

TATAGAATGAGTAGTGGAAGGTAGTTATAAATGTAAGTCAAAAAC
CACACAACCAATTTGAGAAATGAGGAAGGTAATAGTGTTGAATATGTCTT
CTTTATCTTGATATAAATGTATTTGTGCATATATTAACCAGTTTATTTATTT
ATTATTATTTTTTGAGATGAGCTCTCGCCATGTTGCCCAGGCTGGTCTTGA[

FIG. 8.12

A/C]CTCCTGGGCTCAACTGATTCTACCATTTAGTCCTCCGAGTAGCTGGGA
CTACAGGCATGCACCACCATAACCCAGCTGACCAGTTTTTTTCTATTCTCT
ACTTAATTTCTCTACTATAACAATAATATGTGTTAATGGTAGTTAACTTT
ATATCTCAGTATTAAGTCACAAGATATCAAAAAGGGAATGCGACTTA

SG13S397

ATGTCTTCTTTATCTTGATATAAATGTATTTGTGCATATATTAACCA
GTTTATTTATTTATTATTATTTTTTGAGATGAGCTCTCGCCATGTTGCCAG
GCTGGTCTTGAACCTCTGGGCTCAACTGATTCTACCATTTAGTCCTCCGAG
TAGCTGGGACTACAGGCATGCACCACCATAACCCAGCTGACCAGTTTTT[C/T
]CCTATTCTCTACTTAATTTCTCTACTATAACAATAATATGTGTTAATGG
TAGTTAACTTTATATCTCAGTATTAAGTCACAAGATATCAAAAAGGGAAT
GCGACTTAGTTACAAGCAGAATGAATATCACTCAAAGATGAATAAAGAG
AAGAGGGTAGTGCATTTTCTGTTGGATGAGAGAAAGTTTCATTGTT

SG13S377

GCAGTGGCGTGATCCCAGCTCACTGCAATCTCTGCCTCCTGGGTTT
AAGTGATTCTCCTGCCTCAGCCTCCCGAGGGGCTGGGATTGTAGGCGTG
ACCACTATGCCCATCTAATTTTTGTATTTTTAGTAGAGATAGGGTTTTGCC
ATTTTGGCCAGACTGTCTTGAACCTCCTGACCTCAGGTGATCTGCCTGCCTC[
A/G]GCCTCCACAGTTTTGTGATTATAGGCATGAGCCACCGTGCCCGGCCT
TAACCTTTGTTTTCTTACACAACACACTACGTGATGTTTTCCACATGCATG
GGTCATTTGCTTCATTTACGTACAAATGCATAAGCAATATACTGTGTGGTG
TGAGTTTGTGATGGGAAAAGGAAGAAGTTTTGCGGATACTACACTGG

SG13S189

GCCAGGGCTGTTCTCCAACTCCTGGACTCAAGCCATCCTCTAGCCT
CGGCCTTCCAAAGTGCTGGGACTATAGGCGTGAGCCACGGTGCCAGGCCC
TTGACCACATTTTAAACCCCTCTGAACCTCAGTTTCACTTTCTGGGCAATG
GGAGGGGGGTAATTTGTCCCTCAGAGGGTTGCACTGAGGGGGCAAATGTGA
G[C/G]CTCTGGGTACAATGCCAGTACAGACTAGGTCCCCACGACACAGCC
GCTCAGCGGCTCCGGATTCTGGGCTGCTCTGGACTGCGGCCAGGCGGTCT
TCTGCGGGAATCCGGGCAGGCAGGGCGGGCTGCGCTCCCCTCCCCGGCTC
TCCCGGTGCCCTTGTCTTTTTGTTCTGTCTCAGCAGCTCTCTATTAAGAT

SG13S100

TTTTTGTCTGTCTCAGCAGCTCTCTATTAAGATGAATGGCATTTC
AAAGGCTTCACCTCTGATAAGTGTTCTCTGCAGCTGCAGCCAGAATCTTA
ATGTGCGCGCTGTAATTTAATGGCCGTCTCGGCTATTAACACGCTCTTCTC
GGGTGAAGTGGAATCCCTCCATCCCCGGGCCTCTGCACGTGCTCTGCGC[A/
G]CTGGCTGGGGGTGACTCCAAGGAGCTCAGAGCGGGGTGCCCGGCACCT
CTCGCCAGGCGCCTTTCGACCTTCTAAAGCGCGAATGGCTGGACTTTTCTC
CCATGTGTGGGGCCCCAGAAGGTGTGGGGCCCCAGAAGGTGTGGGGTCCC
TGCGTTCCACGGAGCCCGGAAGGTTTCCAGTGATGGTGGGGGCTGACC

SG13S398

GGAGCCCGGAAGGTTTCCAGTGATGGTGGGGGCTGACCACGTTGG
TCCCGTGGGTGCTGTTTTTCATGTGCCGGCAGATTGGGATGAGTTTAAAAG
ACAGAAGCGTGTAGGATAGAGAACTTCTTTAAAAACTGGAAATTTTAAT
CTGGGGATTATAACTATTGGACAGTCAAGTGCAAGAGTGAATACACTTCT
CA[C/G]TCCCTCCTCCCAATTTTTATTTGCGGGATTAGTCAGTCCCCCTCTG
CCACATGATAAATTGTGAGAACTACCAGGGTCTTCATTCTCCTGCCATCTGG
TTGACCTCTCCAAGAATGGACACCCGGGCAGCCTGGGCCAATGAGGCTGT
CCTAAGAGTTTAGATGAGAGAAGTCAGTCTTTGACAGGTGATGGAAGCTG

FIG. 8.13

SG13S94

CAGTGATGGTGGGGGCTGACCACGTTGGTCCCCGTGGGTGCTGTTT
TCATGTGCCGGCAGATTGGGATGAGTTTAAAAGACAGAAGCGTGTAGGAT
AGAGAAACTTCTTTAAAACTGGAAATTTAATCTGGGGATTATAACTATT
GGACAGTCAAGTGCAAGAGTGAATACACTTCTCACTCCCTCCTCCCAATTT
[C/T]TATTTGCGGGATTAGTCAGTCCCCCTCTGCCACATGATAATTGTGAG
AACTACCAGGGTCTTCATTCTCCTGCCATCTGGTTGACCTCTCCAAGAATG
GACACCCGGGCAGCCTGGGCCAATGAGGCTGTCCTAAGAGTTTAGATGAG
AGAAGTCAGTCTTTGACAGGTGATGGAAGCTGTAAAATGTAAAACCTCCA
SG13S101

TAAGAGAAGCTGAGAGAGAGCGAGAGGAGAGATTGGAAGAAAGA
CAGAGACAGAGGTAGAGAGAAGGGAAAGAGAGAGAGAAAAGGGACAGAA
GAGAGAGAAAAAAGAGGGGGCGGGCGCGGTGGCTCACGCCTGTAATCT
CAGCACTTTGGGAGGCCGAGGCGGGCAGATCACGAGGTCAGGAGATCGA
GACCATCC[C/T]GGCTAACACGGTGAAACCCCCGTCTCTACTAAAAAATAT
AAAAAAAATTAGCCAGGCGTGGTGGTGGGTGCCTGTAGTCCCAGCTACTG
AGGAGGCTGAGACAGGAGAATGGCGTGAACCCGGGAGGCAGAGCTTGCA
GTGAGCTGAGATCGCGCCACTGCACTCCAGCCTGGGCAACAGAGCAAGAC
TCCGTCTCA

SG13S95

TCCACCAGCAGCTTTTCTGAGTCTCCAGCTTGCAGATGGCAAACCA
TGAAACTTCATGGTGTCCATGAGCATGTGAACCAATTTCTATTATAAATCT
GCAATATATATATATAGAGGAGACTTATTTATATATTGGTTCAGTTTCTCTG
GAGAGCCTTGGCTAATATAAAGTCTATACTCTACAAAGTGCCCTAGGTAC[
G/T]CAGGGAGTACCCAAGTGTGTCATGACCAGCCCGACAGCCCTGGCTGC
TGGCTTCCCCGCACAACTCTGCACGCTGCCTTCATCAGCCTTTCTCTCT
CAGCTGAACCGAGGGCATTGAAGCGGGCCTCTGGCACTGTACCTATGAGG
GAGCAATATCTTCCCCTACACTGACCTCTTCCGTGCCGAGATGCAGCCC
SG13S102

GCCTCTGGCACTGTACCTATGAGGGAGCAATATCTTCCCCTACACT
GACCTCTTCCGTGCCGAGATGCAGCCCTCCCTGCTGCCACTAGTTACAGTG
GTCCATGTTCCCTTTCAAAGTGAAGTTTTGATAAAAGCACCTCTTAACCAA
TGCCAAATAGCTAAGTCTGGGACAAAGATTGCAGGTATTTTGCATTTTCC[
A/T]TGTAACCTCAGAGGGATTGCCATTACACTGATCTGAGCTGCAGAAT
ACCAGGCAGCCACCTCACCCACCCAGCAGGTCCACTCTTATACTTTCTCAG
AAAGCACAGCCACTCTACTCTTATTCAGTTGAAAAGAATTTCAGGAAGG
TGTTTCTGCGATTGCCTCAGAAAAGTCAGTTCCCTTTGGGAATTTCCCT
SG13S103

TACTTTTCTCTGAAGAAATGGAGATATCAGCTGTCCCTCCCCACTG
CCATTTATTCTTTCCTTCATTCAAACCTTATGTGGCTGCTACTTACCGTGTG
TTAAGTGTTCACTTTTTTTCTTGGAATTCAAAAAAAGAAGGACAGTATTTG
GGGCACAGATCTTTTGGTGTCTATACATTTTTTTAAAGTTTCATTTTA[C/T]
ATTTGTGTGTGCGTGTGTGTGTGTGTGTGAGACAGTCTTGCTCTGTTGCC
AGGCTGGAGTGCAGTGGCATAATCATTGGCTCACTGTAGCCTCAAAGTCC
TGGGCCCAAGCAATCTTCCCACCTCAGCCACCCAAAATGCTGGGGTTACA
GTTTATGCCACTCTGTCTGACCTGAAAGTTTTGGGTTTACTTTCC
SG13S104

GCATAATCATTGGCTCACTGTAGCCTCAAAGTCCTGGGCCCAAGCA
ATCTTCCCACCTCAGCCACCCAAAATGCTGGGGTTACAGGTTTATGCCACT
CTGTCTGACCTGAAAGTTTTGGGTTTACTTTCCCTTCTTTCTTTGCTGAA

FIG. 8.14

GTCAGAGATGATGGCAGCTTCCAGATTCTCTGGTGCCTGTGCTGGGCTC[A/
G]TGCTGGTCATGGTCTTGGGTCCAGGATTCATTCTGGAGACTCTCAGGGA
AGTTTCCCATGACAAGGAAATGTAGGAGAGTGTGCTGGCTTTGCGTGCTC
CTCTGCCAAGCCCTGCTTCTCCTGGTGGGACACACTGAACCACAGCCAGG
GCATTTTGGTGGTTAGTTAAAAAAAAAAAAAAAAAAAAAAAAAAGGAAG
SG13S191

CTTCAGAAATTGTAATGATGAAAGAGTGCAAGCTCTCACTTCCCCT
TCCTGTACAGGGCAGGTTGTGCAGCTGGAGGCAGAGCAGTCCTCTCTGGG
GAGCCTGAAGCAAACATGGATCAAGAACTGTAGGCAATGTTGTCTGT
GGCCATCGTCACCCTCATCAGCGTGGTCCAGAATGGTAAGGAAAGCCCTT
CA[A/C]TCAGGGAAGAACAGAAGGGGAGATTTTCTTTGATGGTTGTTTGA
AGTCAGGCTTAAACAATTGTGTCTGTGTGTGCGCATGCACAAACACTTTTA
CCTTATCTTTATTTTCTTCTTTTATTTGAATGTATAGGGTTGTGTGTATTT
TGTGTAAATTTGGGGTTTTCTCTCTTAGTCTTCACTTTTGTGGTG
SG13S105

TTTTCTAACATCTGCAGTGCAATTGAAGTTACCAGTCATCTGCAGTC
TAAAAAGAAAGTGATTTTGGGAGGTGCGTAGAAAAAATCATCTTATTATT
TTTCTCTATATTACTTTTTTCTTTTTTCTCCTGAAGAACTTTTTTTTTTG
GTGATACCTTCTTTTTCTTAGCACGTATAATTTTGGAAAGCATTTTTC[A/G]
TATGCAGTGTATACTTCAGAAAGAGAGAGAGAGAGAGAGGAAAATTGTCCTG
TTCAGCGTTTGCATTTCCATTATTCCTGCTATTAGTTAAAAACAACAACAA
CAACAAAAACAAGCAGGATACCTAGATCTGGAAAAGGGAGAATTGTGT
AGAGCTGTCTTCCTAAAGTTCTGAGTTAGGGCTGCCTCAGACCACTT
SG13S106

TTTTGGAAGCATTTTTTCATATGCAGTGTATACTTCAGAAAGAGAGA
GAGAGAGAGGAAAATTGTCTGTTACGCGTTTGCATTTCCATTATTCCTGC
TATTAGTTAAAAACAACAACAACAAAAACAAGCAGGATACCTAGA
TCTGGAAAAGGGAGAATTGTGTAGAGCTGTCTTCCTAAAGTTCTGAGTTA
GG[A/G]CTGCCTCAGACCACTTTCATAACTATCTCCAGTGGCTTTGTGTTTT
ATATTTATTAAGATAGAGAAAAAAGAGTAATTACTAAGGGCAGCTGCTG
TAGCTTTATGGTGATTACTGAACATTGACATGCTGTCACGTTTTTGGAACT
TTGAGTATTTAATCACTTTGGGATATTCTATTTTCCCCCATCTTGAGTGT
SG13S107

GGAACCTTGAGTATTTAATCACTTTGGGATATTCTATTTTCCCCCAT
CTTGAGTGTGGACAGATGCTGGTGATGTAGCCTTCTGGGCACAGAGCAAG
CCTCCCCCTCAGCCTCTGCACCAGAAAGGCTCAGCTTCACACACTCCAAGT
ATGTTTTCTACAAGAACTACACTTTGTGGCTTTCTGACCCAAACATTTTT[A/
G]TACTAAATTACACACAACAAAGTTGTAGCTCAGAGAGGGAACAAATGG
CTTATTTAGGCCACCATTTTCTTGAGCCATTATGATTTACACAGGGCTCC
CTTGCCCTGTAAATTGGCAAGGATTCCATTATTCAACCCGCATACATGTA
CAGAGACCCTGCTCTGGCCCAGATAGTATTCTGGGTACAGGCGGATA
SG13S108

TGTGGACAGATGCTGGTGATGTAGCCTTCTGGGCACAGAGCAAGCC
TCCCCCTCAGCCTCTGCACCAGAAAGGCTCAGCTTCACACACTCCAAGTAT
GTTTTCTACAAGAACTACACTTTGTGGCTTTCTGACCCAAACATTTTTATA
CTAAATTACACACAACAAAGTTGTAGCTCAGAGAGGGAACAAATGGCTTA
[C/T]TAGGCCACCATTTTCTTGAGCCATTATGATTTACACAGGGCTCCCT
TGGCCCTGTAAATTGGCAAGGATTCCATTATTCAACCCGCATACATGTACA
GAGACCCTGCTCTGGCCCAGATAGTATTCTGGGTACAGGCGGATAGAGCA
GGAACAAAAACAGCTACAGTGATGGACAGGTCAGCCTGCAGCAATGCC

FIG. 8.15

SG13S109

TTTTTATACTAAATTACACACAACAAAGTTGTAGCTCAGAGAGGGA
ACAAATGGCTTATTTAGGCCACCATTTTCTTGAGCCATTATGATTTTCACAC
AGGGCTCCCTTGGCCCTGTAAATTGGCAAGGATTCCATTATTCAACCCGCA
TACATGTACAGAGACCCTGCTCTGGCCCAGATAGTATTCTGGGTACAGGC[
A/G]GATAGAGCAGGAAACAAAACAGCTACAGTGATGGACAGGTCAGCCT
GCAGCAATGCCTGCAGTCTCTGCAAAGGTAGCTGTATGGGTGGGCAGGTG
GCTAGCACTTATTTCAGCTCTGGAAGGATCTCCCCTCTGGCCTCTCCCCTGA
CACCCATCAATAAAACTGAGGAGCATCGGTGGACAGGGGACCTTGTGCCC
SG13S110

TTTTCTTGAGCCATTATGATTTTCACACAGGGCTCCCTTGGCCCTGTA
AATTGGCAAGGATTCCATTATTCAACCCGCATACATGTACAGAGACCCTG
CTCTGGCCCAGATAGTATTCTGGGTACAGGCGGATAGAGCAGGAAACAAA
ACAGCTACAGTGATGGACAGGTCAGCCTGCAGCAATGCCTGCAGTCTCTG
C[A/G]AAGGTAGCTGTATGGGTGGGCAGGTGGCTAGCACTTATTTCAGCTCT
GGAAGGATCTCCCCTCTGGCCTCTCCCCTGACACCCATCAATAAAACTGA
GGAGCATCGGTGGACAGGGGACCTTGTGCCCCCTCCCTGCCTGTGCAGTT
GGGGCTGAACCCAGCTACGAAGTTTGAGCTCACTCTCTCCAGCTCCCTCTC
SG13S111

GACAGGTCAGCCTGCAGCAATGCCTGCAGTCTCTGCAAAGGTAGCT
GTATGGGTGGGCAGGTGGCTAGCACTTATTTCAGCTCTGGAAGGATCTCCC
CTCTGGCCTCTCCCCTGACACCCATCAATAAAACTGAGGAGCATCGGTGG
ACAGGGGACCTTGTGCCCCCTCCCTGCCTGTGCAGTTGGGGCTGAACCCA
GC[C/T]ACGAAGTTTGAGCTCACTCTCTCCAGCTCCCTCTCAATTCAGAGCT
GAACTGTGGGAAGCTTCAGAGCTCTCTGTTTCAAGGACAGGTTCTCCTCAC
CTCTCCTAATGGAGGTGCACCAGGGAAGTGGCCCTGCTCTGCCCAGGGCT
TTCTCCTGGACTTTGCCATCATGGTCTAGCAAACCCTGTTTCAGATTGAGG
SG13S112

CACTCTCTCCAGCTCCCTCTCAATTCAGAGCTGAACTGTGGGAAGC
TTCAGAGCTCTCTGTTTCAAGGACAGGTTCTCCTCACCTCTCCTAATGGAG
GTGCACCAGGGAAGTGGCCCTGCTCTGCCCAGGGCTTTCTCCTGGACTTTG
CCATCATGGTCTAGCAAACCCTGTTTCAGATTGAGGTGAGTGGTGAGATT[
C/T]GAATTCTTTTTGACAGATAGGATTAAGTCTTCTTCTGTGGGACAAGTG
GGAGGTAGAGGTAAGATTAAAGATGGCCAAATGTCTGAGTCCTGACAGCC
ACAATATGGAGATCTAGACTTTTTACAGACCACAGGGCACAGGGGCCTCA
CTAACAGAGTTCCCGGAAGTGATGAGTGTGCTGGGGGCTTCCTGGTTGA
SG13S113

TAGGATTAAGTCTTCTTCTGTGGGACAAGTGGGAGGTAGAGGTAAG
ATTAAAGATGGCCAAATGTCTGAGTCCTGACAGCCACAATATGGAGATCT
AGACTTTTTACAGACCACAGGGCACAGGGGCCTCACTAACAGAGTTCCCG
GAAGTGATGAGTGTGCTGGGGGCTTCCTGGTTGAAGAGACACTAGAATGG
AC[C/G]AGCTGGGAGCTAATTTTTTGGGCTGGAGTGTGATGGCCTGCACAT
CACTGCCTCTGTCCCTCCATTGTACAGCTGCCCTTAGGAGCCAGCTGAG
GCAATTTGTGGTCAGAGTGACTTTGCACAGTTGTCCTGCCTGTGTTTCAGGA
AGGGAGTTTCTGTGGTCCCTTTGAAACCACAGAAGAGCCCCCTCGTATAGC
SG13S114

AGTTGTCCTGCCTGTGTTTCAGGAAGGGAGTTTCTGTGGTCCCTTTGA
AACCACAGAAGAGCCCCTCGTATAGCTCTCAATGGAGGGGGCAAACATT
CAAATAACTCAGGAGATAACACAACCTATTTGTTTTTAAGTGTGAGTTTTTA
GGCAATCACAAAGATCCAGATGTATGTCCAAGCCTCTCTTTGCAATTCTA[

FIG. 8.16

A/T]TTAACCTCAATGTTGCAACCATAGACCTACCTTACAGAGTTCAAAAA
AATATGCAAAAACCCTGCCTTTCTTCTTCCTCATACCCCAAATGCCATTC
TGAACATTTCTGTTAGTTAAAAAAGATTTCATGGTGTTACCAGGCACT
GTACACAGTCTGTGTCCCAAGACAAGGAGGTACAGTTCCACATGCGCC
SG13S115

AGGGGGCAAAACATTCAAATAACTCAGGAGATAACACAACCTATTT
GTTTTTAAGTGTGAGTTTTTAGGCAATCACAAAGATCCAGATGTATGTCCA
AGCCTCTCTTTGCAATTCTAATTAACCTCAATGTTGCAACCATAGACCTAC
CTTACAGAGTTCAAAAAAATATGCAAAAACCCTGCCTTTCTTCTTCCTCAT
[A/T]CCCCAAAATGCCATTCTGAACATTTCTGTTAGTTAAAAAAGATT
CCATGGTGTTACCAGGCACTGTACACAGTCTGTGTCCCAAGACAAGGAGG
TACAGTTCCACATGCGCCCATGACTGGGTTGGGCTCTGCACTCTCTCTATA
CTTTGAGAGCCTGATTTTCTGTGATTGGGCAGAGCTGGCCACCTGGTG
SG13S116

TCTGCACTCTCTCTATACTTTGAGAGCCTGATTTTCTGTGATTGGGC
AGAGCTGGCCACCTGGTGCAATGTCCTCCTCTGCCTTTCAAACATGTTTT
AGTCATCAAGATCTTCAAATTTGTAACCCTTTCCAGCTTGATCCAGCAGAA
TGCAGATTTGGAAAAACAGAACGAGTTTAAAAATACATGATTCTAAGAAA[
C/T]CTGGACCAGAACTATCAAACTTGGTTTCCCAGAGAATATAGCAAAT
GGGCTCATTGGCCAATACTATGACATTGGCTTTTGAGAAAAGAAAGGCTT
TATTGCAAGGCTGGCCAGCAAGGAGACAGGAGTTGGGCTCAAATCTGTCT
CCCCAGTTTGGGGCTTAGGGCAAGTTTAAATTACACAGACGCATTTCTTA
SG13S117

AACCCTTTCCAGCTTGATCCAGCAGAATGCAGATTTGGAAAAACAG
AACGAGTTTAAATAACATGATTCTAAGAAACCTGGACCAGAACTATCAAA
ACTTGGTTTCCCAGAGAATATAGCAAATGGGCTCATTGGCCAATACTATG
ACATTGGCTTTTGAGAAAAGAAAGGCTTTATTGCAAGGCTGGCCAGCAAG
GA[A/G]ACAGGAGTTGGGCTCAAATCTGTCTCCCCAGTTTGGGGCTTAGGG
CAAGTTTAAATTACACAGACGCATTTCTTATGAGTAGCAGGCAGAGAGCC
TCCAACTTCTTCTGCCTAGGTACCAGCAGCTTAGACATGATGCAAACCTGG
GAAGCACATACTGTATTTGGAGAAAGTGATTGGGAAGAAATGTGAGCTGA
G
SG13S118

TACATGATTCTAAGAAACCTGGACCAGAACTATCAAACTTGGTTT
CCCAGAGAATATAGCAAATGGGCTCATTGGCCAATACTATGACATTGGCT
TTTGAGAAAAGAAAGGCTTTATTGCAAGGCTGGCCAGCAAGGAGACAGG
AGTTGGGCTCAAATCTGTCTCCCCAGTTTGGGGCTTAGGGCAAGTTTAAAT
TA[C/T]ACAGACGCATTTCTTATGAGTAGCAGGCAGAGAGCCTCCAACTTC
TTCTGCCTAGGTACCAGCAGCTTAGACATGATGCAAACCTGGGAAGCACA
TACTGTATTTGGAGAAAGTGATTGGGAAGAAATGTGAGCTGAGGGGAGG
GGCTCAGTGCCCCTGAGCTACACTTAGTGATGGCAGAGGAAGGATGTCCT
CCC
SG13S119

TGGGGCTTAGGGCAAGTTTAAATTACACAGACGCATTTCTTATGAG
TAGCAGGCAGAGAGCCTCCAACTTCTTCTGCCTAGGTACCAGCAGCTTAG
ACATGATGCAAACCTGGGAAGCACATACTGTATTTGGAGAAAGTGATTGG
GAAGAAATGTGAGCTGAGGGGAGGGGCTCAGTGCCCCTGAGCTACACTTA
GT[A/G]ATGGCAGAGGAAGGATGTCCTCCCGCAGGAGGCTGTTCCACATCT
GCTCTGGTTGTAGGGGGAGCTGGCAGGCATTAGCAGCGGCCTCTTTCCCC
CAAGAGAGGCAGCCTCCTCCAAGTTTGGCGACATTATGGCCCTGCAATC

FIG. 8.17

ATAAGGGTTTGTGAGCATAGTGCTAAGGAGGGAAATGGAGCTGCTGTTAC
TA

SG13S120

CCTCCTGAGTAGCTAGGACTACAAGCATGTGCCACCACGCCCAGCT
AATTTTTGTATTTTGTAGTAAGGACAGGGTTTCACCATGTTGGCCAGGTTGG
CCTCCAACCTCCTGACCTCAAGTCATCCTCCTGCCTCGACCTCCCAAAGTGC
TGGGATTACAGGCATGAAACCAGCCTAGAAATACATACTATTATTTATTC[
C/T]TGTTTTACAGATAAGCAAAGTGAGTCATGGAGAATTTGGTTGAAAGT
CCCAAGGTCAGGAGTCGTGAAGCTGGGATTAAACCTAATCATCTGACTT
TAGAGAGTAGACACTTGCTCCATGCATATTGCCTCCAATTCATTCAATCAA
GCACTCCCTGCTCAAGAAGTTCCTTCTTATGTTGAGCTGAAATCTGCAG

SG13S121

TCATCTGACTTTAGAGAGTAGACACTTGCTCCATGCATATTGCCTCC
AATTCATTCAATCAAGCACTCCCTGCTCAAGAAGTTCCTTCTTATGTTGAG
CTGAAATCTGCAGCCCTATGCGTTTTACCCAGCAGTCCTGGTGCTGTTCCC
TAAATCACTTAGACTGTGCCTGCTCTTCTGTGTTTACAGTGTGAGCT[A/
G]TAATATCCCCCTCTTCGGCCTAACGTTTCTGAAGTCCCTTGCCACTGGGT
CTCCTCTCCTCTTCCTGTGTTCTTTCTAAGAACACCTATGCAGATAGGTGTC
TTCTGTACAGGGAAGCTGTTCCCTGAGATCCGGGCATCGACTCTGTTAGAAT
AATCTACGTATGAGTTATTTTTTTGAGAACTATGTGTCATTGCT

SG13S122

ATGTTGAGCTGAAATCTGCAGCCCTATGCGTTTTACCCAGCAGTCC
TGGTGCTGTTCCCTAAAATCACTTAGACTGTGCCTGCTCTTCTGTGTTTAC
AGTGTGAGCTGTAATATCCCCCTCTTCGGCCTAACGTTTCTGAAGTCCCTT
GCCACTGGGTCTCCTCTCCTCTTCCTGTGTTCTTTCTAAGAACACCTAT[A/G
]CAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCCTGAGATCCGGGCATCG
ACTCTGTTAGAATAATCTACGTATGAGTTATTTTTTTGAGAACTATGTGTC
ATTGCTGACTCATATTAACCTCTGTGGTTAACTAAAATCTCAAGATCTCTTT
ATGTTTGTTGAGAACTTATTTAACTTCTCTGGCCCTCCGTTTCC

SG13S123

GTCCTGGTGCTGTTCCCTAAAATCACTTAGACTGTGCCTGCTCTTTC
TGTGTTTACAGTGTGAGCTGTAATATCCCCCTCTTCGGCCTAACGTTTCTG
AAGTCCCTTGCCACTGGGTCTCCTCTCCTCTTCCTGTGTTCTTTCTAAGAAC
ACCTATGCAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCCTGAGATC[C/T
]GGGCATCGACTCTGTTAGAATAATCTACGTATGAGTTATTTTTTTGAGAA
CTATGTGTCATTGCTGACTCATATTAACCTCTGTGGTTAACTAAAATCTCAA
GATCTCTTTATGTTTGTTGAGAACTTATTTAACTTCTCTGGCCCTCCGTTT
CCTTCACTGAGCAGTGGAGTGATTGATAACCTCCACCTGTGGTT

SG13S43

CACCTATGCAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCCTGAG
ATCCGGGCATCGACTCTGTTAGAATAATCTACGTATGAGTTATTTTTTTGA
GAACTATGTGTCATTGCTGACTCATATTAACCTCTGTGGTTAACTAAAATCT
CAAGATCTCTTTATGTTTGTTGAGAACTTATTTAACTTCTCTGGCCCTC[A/
C]GTTTCCTTCACTGAGCAGTGGAGTGATTGATAACCTCCACCTGTGGTTG
CTGAAGGTCTTGACACAAGATGATATAGTTAAAGTAGCTAGCAGTGCCAC
GTACGGCGGATGCCTCACACGGTTTGACAGCCATCTCTCTATCTGTGTCTT
TGTCTCTCTCACACTGGTTTTGGCTTACTGTTAGCAGCTAGCCGA

SG13S399

TCTGTGGTTAACTAAAATCTCAAGATCTCTTTATGTTTGTTGAGAAA
CTTATTTAACTTCTCTGGCCCTCCGTTTCCTTCACTGAGCAGTGGAGTGATT

FIG. 8.18

GATAACCTCCACCTGTGGTTGCTGAAGGTCTTGACACAAGATGATATAGTT
AAAGTAGCTAGCAGTGCCACGTACGGCGGATGCCTCACAACGGTTTGC[
A/C]GCCATCTCTCTATCTGTGTCTTTGTCTCTCTCTCACACTGGTTTTGGCT
TACTGTTAGCAGCTAGCCGAGATAAGTGTGTTTATGGTCTTTGCATGTATT
GTTTCTGTAGCATACTGGAGGATTACAAGAGGTTGGGGAGTGAGGGGGCG
GTGAGGAGTAGACAAAGGCAGCCAACTCTTCCAAGTTTAGCTTAGAA
SG13S124

TTGATAACCTCCACCTGTGGTTGCTGAAGGTCTTGACACAAGATGAT
ATAGTTAAAGTAGCTAGCAGTGCCACGTACGGCGGATGCCTCACAACGG
TTTGCAGCCATCTCTCTATCTGTGTCTTTGTCTCTCTCTCACACTGGTTTTG
GCTTACTGTTAGCAGCTAGCCGAGATAAGTGTGTTTATGGTCTTTGCATG[
C/T]ATTGTTTCTGTAGCATACTGGAGGATTACAAGAGGTTGGGGAGTGAG
GGGGCGGTGAGGAGTAGACAAAGGCAGCCAACTCTTCCAAGTTTAGCTTA
GAAGGAAGGAGCGGTAAACCCTAGTTGAATGTTGGACTGAAGCAGGTTTG
TTTTGTTTTGTTTAAAGGATAGGGAAGATCTGTGCGTGTTTCCAGGATA
SG13S125

ACTTGAAGTCAGTGGCATGGACAGGGTCAAGATCACAGTTAGAGG
ATGCAGCCTTAGAGAAAAGGAAGGGGCTCGGTTCTCTGAGCAAGGAGGG
AAAGAAGAGAGGCAGATGCAGAGAAGTACGGCACATCGTGCTGCTGGTT
GTAGAAATAACCTCTGACTTTTAATAAAGTCATCCCTCGGTATCCCTGGGG
GATT[A/G]GTTCTATGACCTCCCTCGGATGCCAAAATTTCGTGGATGCTCAA
GTCCCTGATATAAAATGGCATAGTATTTGCATTTAACCTACACACATCCTC
CATATCCTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGTGAGATGGAGT
CTTGCTCTGTGCGCCTGGCTGGAGTACAGTGGCTCGATCTTGGCTCACT
SG13S400

AATACCTGATAGAATGTAAATGCTATGTAAACAGTTGTTATACTGT
ATTGTTAAAAGACAGTAACAAGAAAAAAATCTGTACATGTTCAAGTCCAG
ACAAATGGTTTTCTGTTTTTTTTTTTTTTTTTTTAAATATTTTTGGTCAAGTGGT
GGTTGACTCCAGGAATGCAGAACCCGCAGATATAGAAGGTTGATTATGC[
A/G]TTCAGAGGCAGGGAATACCATCTTGGGTTCAGAAAAGAAAATGATCA
GCATTTTCTGTACATACTCTGGTAAAAACAGATCTTTTGAATGGACAGGTGT
ATTAAACCCTGTGGAGCTGGCTGGGCTGGCGGCTCACGCCTGTAATCCC
AGCACTTTGGGAGGCTGAGGCAGGTGGATCACGAGGTCAGGAGTTCGAG
SG13S126

TGCCCCGCAGAGTTTGAAGTCCCGGCTGCACCTCTCCCCAGCAGCA
GGTTGACTCTGGAAAGTTGCAGCGTTCTTACCTACAGAGTGGGAACAGTA
CTACCCATTGCACAGAGTGGGTGCAAAGCTCTGTGACGGAATACATGGCA
AGTGCCCAACCATTTGCCTGGGATGAGGTGGGCCCTTCCTTTACGTAAGA
GA[A/G]CCCTACAGATACACTCAAAGTGGGCACATTCCTACAGAAGGAGT
GTTATTTGTGTAGAAAAGAAAAACATGAAAGGCTTTTATTCCTATACACA
ATAAAGCACCCCTTTAATGTCTTTTTGAGGAGGATAATATGAAATTGATGA
AAAGGAACCCTGTGGTTGGATCCCTGACAATCACATGTATCCCTTTTTTCA
C
SG13S127

TACAGATACACTCAAAGTGGGCACATTCCTACAGAAGGAGTGTTAT
TTGTGTAGAAAAGAAAAACATGAAAGGCTTTTATTCCTATACACAATAAA
GCACCCCTTTAATGTCTTTTTGAGGAGGATAATATGAAATTGATGAAAAG
GAACCCTGTGGTTGGATCCCTGACAATCACATGTATCCCTTTTTTCACTCT
T[A/G]AAAAAGGAGTAAAGGAATAAAATAGAAANNNNNNNNNNNNNNNNNN
NN

FIG. 8.19

FIG. 8.20

SG13S193

GCTCCTGAACATGCCCCACAATGAACCAGATGCAAACCTTTTCCCTT
GGCAGGATTCTTTGCCCATAAAGTGGAGCACGAAAGCAGGACCCAGAAT
GGGAGGAGCTTCCAGAGGACCGGAACACTTGCCTTTGAGCGGGTCTACAC
TGCCAAGTGAGTCCTAACCCTGATGTTGCTAATAAGTGGGGGCATGGGCA
GGG[A/G]GGCCTCCTTCTAGGAGTGATGACCACCCTTAATACCACATGTCT
GTCTGAGCCAAGTTTCTGAGCGCCAGGGAGGTGAGGAAGGTTGGACTTCA
CCAGAGAGGCTTTGTGGACACCCTTTATCATCTTAGTGAGTGCTAGTGTCA
AAACAAAGGGAGTGGGGATATGGGGCACATTGGTGGAGGGAGGTGTGAT
CTC

SG13S88

TTGCCCATAAAGTGGAGCACGAAAGCAGGACCCAGAATGGGAGGA
GCTTCCAGAGGACCGGAACACTTGCCTTTGAGCGGGTCTACACTGCCAAG
TGAGTCCTAACCCTGATGTTGCTAATAAGTGGGGGCATGGGCAGGGGGGC
CTCCTTCTAGGAGTGATGACCACCCTTAATACCACATGTCTGTCTGAGCCA
AG[C/T]TTCTGAGCGCCAGGGAGGTGAGGAAGGTTGGACTTCACCAGAGA
GGCTTTGTGGACACCCTTTATCATCTTAGTGAGTGCTAGTGTCAAAACAAA
GGGAGTGGGGATATGGGGCACATTGGTGGAGGGAGGTGTGATCTCTGCAG
CTTCAGAAAGATCTGAAAGAGTCATTTGGTTAGAGAAGTTGACCTATTTCC
T

SG13S131

AAACAAAGGGAGTGGGGATATGGGGCACATTGGTGGAGGGAGGTG
TGATCTCTGCAGCTTCAGAAAGATCTGAAAGAGTCATTTGGTTAGAGAAG
TTGACCTATTTCTGTGGGGTTAGACCAGGGTTGCTACTGTGAACACCAGC
CATGACTCACCAGTCACCTTCAGAAGCCACAGGCAGGACATGCTGACGAC
AG[C/T]CTTCAACTCACCCACCCCTTGCTCCCCTGCGGGTGGAAGTCTGGA
GGTGACACCACTGCATTTTCTAACACGGGGGCTCCTTGAGCAACTAGAAC
AAGAACAGAAAGAATGGGGACATTAGCAGGTGCTTTCCCCCTCTCTCATT
CTTTTCTTTGAATAAAAAGGTTGTTTGAACACCTGAGCGGCTCCTAAAG
A

SG13S132

CTCCTCTCTTCTTTATGCAGAGTGATTTCAAGGCTCAGCCAGTGGC
AGGCATGCTGGGGACTATGGACTACGGACTAGGGGCCTGTCACAGAGGA
AGGCCTCATGCTAGAGAGCTAAGGGAGGAGCTGGCCTTCAGTTCATCCC
AGGAGCAACTTTGATGTTCCCAGAGATCCTTCCAAAGGGGGAGTCATGGT
CA[A/C]CCAAGAAAAATGTATTCAGAATGCCAAGAATGGTGCAAACCTCAG
GACAAAGATTCACTGCAGGGTTGGAGTCCCTGGGCTTGCTGCTGGCAC
CATGGGAGGGAGGGTCCCCTTCAGGGGTACCGTTGGTTTCCTGTGAATTA
AACTGGCTTCAAGGGATCTCGACTGAACAGGCCTATATCACACTCACTGA
TAT

SG13S133

TCTCCTCATCTAGGTATTTTAAATTGTTTCAGTGAGGTGTAGGCATG
AGGGGATTGGAGGGGGCATCTCCTCCATTGCAGTTTTTCATTGGCTGCTTT
GCTCCCTCAGCTCCGAAATCGCTGGGCCACTCTCGAACGCATTAGTACGG
TAGTCACAGGTTGATTGCCTGGCCCCTTGCCCTCTGTGGGCATTTTCCCT[C
/T]TCAGACAGCCCCTGAGTACTCACAGTGCTGCTACAGTGGGCCACCTAG
ATCTCCCTCTTTCTCCATGCTCCCACGTGCTCTGGGCTCCACTCCCTTCTCC
CAAGCACTTCTGTCCAGGGCTATTCCAGCAGTCTGACCTCAAGGAAATCC
TTTGCTAAACTGATTATAGAGAGGTTTCTATTTTAACATTTAGGTCT

FIG. 8.21

SG13S38

ATCTAGGTATTTTTAATTGTTTCAGTGAGGTGTAGGCATGAGGGGA
TTGGAGGGGGCATCTCCTCCATTGCAGTTTTTCATTGGCTGCTTTGCTCCCT
CAGCTCCGAAATCGCTGGGCCACTCTCGAACGCATTAGTACGGTAGTCAC
AGGTTGATTGCCTGGCCCCTTGCCCTCTGTGGGCATTTTCCCTTTCAGAC[A
/T]GCCCCTGAGTACTCACAGTGCTGCTACAGTGGGCCACCTAGATCTCCCT
CTTTCTCCATGCTCCCACGTGCTCTGGGCTCCACTCCCTTCTCCCAAGCACT
TCTGTCCAGGGCTATTCCAGCAGTCTGACCTCAAGGAAATCCTTTTGCTAAA
CTGATTATAGAGAGGTTTCTATTTTAACATTTAGGTCTTCCATGT

SG13S134

AGGTGTAGGCATGAGGGGATTGGAGGGGGGCATCTCCTCCATTGCA
GTTTTTCATTGGCTGCTTTGCTCCCTCAGCTCCGAAATCGCTGGGCCACTC
TCGAACGCATTAGTACGGTAGTCACAGGTTGATTGCCTGGCCCCTTGCCCT
CTGTGGGCATTTTCCCTTTCAGACAGCCCCTGAGTACTCACAGTGCTGCTA
[C/T]AGTGGGCCACCTAGATCTCCCTCTTTCTCCATGCTCCCACGTGCTCTG
GGCTCCACTCCCTTCTCCCAAGCACTTCTGTCCAGGGCTATTCCAGCAGTC
TGACCTCAAGGAAATCCTTTGCTAAACTGATTATAGAGAGGTTTCTATTTT
AACATTTAGGTCTTCCATGTATTAATTCTCAGAATCAATTTAAGATG

SG13S135

CCTTTCAGACAGCCCCTGAGTACTCACAGTGCTGCTACAGTGGGCC
ACCTAGATCTCCCTCTTTCTCCATGCTCCCACGTGCTCTGGGCTCCACTCCC
TTCTCCCAAGCACTTCTGTCCAGGGCTATTCCAGCAGTCTGACCTCAAGGA
AATCCTTTGCTAAACTGATTATAGAGAGGTTTCTATTTTAACATTTAGG[C/
T]CTTCCATGTATTAATTCTCAGAATCAATTTAAGATGTTTAAAGGTGTGAT
TTAAGACATTTTAAAACCATTTGGAGGAGAGTACAGAAATTATGTCACTT
GCTGTGACGCTCTTTGCACCATCTGCAGAGAAAGATACTAGAGTCCCGCC
TTGGACACATCCACATGCAAGAGGTGCAAAGAAGGTGTCTTTGATGA

SG13S136

TTCTCAGAATCAATTTAAGATGTTTAAAGGTGTGATTTAAGACATTT
TAAAACCATTTGGAGGAGAGTACAGAAATTATGTCACTTGCTGTGACGCT
CTTTGCACCATCTGCAGAGAAAGATACTAGAGTCCCGCCTTGGAACATC
CACATGCAAGAGGTGCAAAGAAGGTGTCTTTGATGAGGCAAGGTCAAAA
CT[C/T]CTCCCCAGACGAAATCCAAAGAAGCATTCTACTATGCTATATC
AGTTTGGAAGAAAAAAGTTCTGCCAGGTGACTGCATTCTCACTGGTCACA
TTGTGTTTCTATGGACTCCTCAGCTCAACCAATTTGGAGAAGTTATGGTGC
AATTTACCATATCTGGTTAGAAGTTAAGTTTCCAATTTGCTGGCAATGAA
SG13S137

AAGAAGGTGTCTTTGATGAGGCAAGGTCAAAACTTCTCCCCAGACG
AAATCCAAAGAAAGCATTCTACTATGCTATATCAGTTTGGAAGAAAAA
CTTCTGCCAGGTGACTGCATTCTCACTGGTCACATTGTGTTTCTATGGACT
CCTCAGCTCAACCAATTTGGAGAAGTTATGGTGCAATTTACCATATCTGG
[C/T]TAGAAGTTAAGTTTCCAATTTGCTGGCAATGAAGAAGAAATGGAGCA
GGCCAGGCTGTGTAGTTTCTGCCACGTGCCCCCGGGAGTGAACAGCTCTG
TTTGTAAGAAGCCATGGTGCTTAGACCTGGGCTCGCTAGTTGCCAGCCTCC
AAATTGCAGAAGTGCCCTTTGGTTGGTGGCTATGCTGTGTCACTTGGGA
SG13S86

GCAACATATCTGTGTGCCTGTCTGGGTTGTAAAAAGGGTCAAAGAT
CAATGCAGCAGGCAGCTACATGCTGGCAAAAGCCAGAGGCAGCTGGTCT
GTTTGCCTGTGCCAGGAAACCACTGGGAATGGGGTTGTGTGTTATTCTAGG
AGAAAGTCGTCCCAGCAGCAGCTTCTCCAGGGGCATCCAAGAGCACTGAA

FIG. 8.22

AA[A/G]GGTTGCAAGATGACCCATGAGGCTGCAGGAAGAAAAGAACATGC
ATTTAATCTTGCTATCTGAAAAGTAAGACATGAAGCTTTCCTCATTTTAA
TATACACATGGACAGTAGTATGTGTATATAGTTTATATGCAAATATACTTG
TTATAAGGTTGCATGCTCAAAATTTTTGGTTCATGGGGTGTGGGATCATAA
SG13S87

CAGCTACATGCTGGCAAAGCCAGAGGCAGCTGGTCTGTTTGCCTG
TGCCAGGAAACCACTGGGAATGGGGTGTGTGTTATTCTAGGAGAAAGTC
GTCCAGCAGCAGCTTCTCCAGGGGCATCCAAGAGCACTGAAAAGGGTTG
CAAGATGACCCATGAGGCTGCAGGAAGAAAAGAACATGCATTTAATCTTG
CT[A/G]TCTGAAAAGTAAGACATGAAGCTTTCCTCATTTTTAATATACACA
TGGACAGTAGTATGTGTATATAGTTTATATGCAAATATACTTGTTATAAGG
TTGCATGCTCAAAATTTTTGGTTCATGGGGTGTGGGATCATAAATGTTTAG
GGACCATGGCTATCAAGGAAAAACAGCATGAAGGATAAATGATACTGGT
G

SG13S138

CTATCTGAAAAGTAAGACATGAAGCTTTCCTCATTTTTAATATACA
CATGGACAGTAGTATGTGTATATAGTTTATATGCAAATATACTTGTTATAA
GGTTGCATGCTCAAAATTTTTGGTTCATGGGGTGTGGGATCATAAATGTTT
AGGGACCATGGCTATCAAGGAAAAACAGCATGAAGGATAAATGATACTG
G[C/T]GGATTAAAAAGACAGATGCATGTATTTTAGCATAAAACACAACCTG
CTGACTGATACAGATAGCTCAAGATTCTGGGGCAGCTGCTGAACAGATAC
ACTAGCCAGTGTGGCTCATCGGCTCAGACTTGGCCTTAATTAATGGGCTGT
CCCTCCACCCATCTCCCATGAGGGCAGAGCTGAGCCAGGGTTTGAGAGCT
SG13S139

AGTTTATATGCAAATATACTTGTTATAAGGTTGCATGCTCAAAATTT
TTGGTTCATGGGGTGTGGGATCATAAATGTTTAGGGACCATGGCTATCAA
GGAAAAACAGCATGAAGGATAAATGATACTGGTGGATTAAAAAGACAGA
TGCATGTATTTTAGCATAAAACACAACCTGCTGACTGATACAGATAGCTC
AA[C/G]ATTCTGGGGCAGCTGCTGAACAGATACACTAGCCAGTGTGGCTCA
TCGGCTCAGACTTGGCCTTAATTAATGGGCTGTCCCTCCACCCATCTCCCA
TGAGGGCAGAGCTGAGCCAGGGTTTGAGAGCTAAAAGGAATTGGACCTG
GACTCTGTTCACGTGTATATTTTAATTCTAATTAATTCAATTCTTTTGAAAGA
SG13S140

GTATTTTATAGCATAAAACACAACCTGCTGACTGATACAGATAGCTCA
AGATTCTGGGGCAGCTGCTGAACAGATACACTAGCCAGTGTGGCTCATCG
GCTCAGACTTGGCCTTAATTAATGGGCTGTCCCTCCACCCATCTCCCATGA
GGGCAGAGCTGAGCCAGGGTTTGAGAGCTAAAAGGAATTGGACCTGGAC
TC[A/G/T]GTTACGTGTATATTTTAATTCTAATTAATTCAATTCTTTTGAAAG
ACAGAGTCACACTCTGTTGCCTAGGCTGGAGTGCAGTGGCACGATCTTGG
CTCACTGCAACCTCGGCCTCCAGGTTCAAGTTATTCTCCTGCTTCAGCCT
CCTGAGTAGCTGGGATTATAGGCACATGCCCCCATGCCTGACTAATTTT
SG13S141

GCTAAAAGGAATTGGACCTGGACTCTGTTACGTGTATATTTTAAT
TCTAATTAATTCAATTCTTTTGAAAGACAGAGTCACACTCTGTTGCCTAGGC
TGGAGTGCAGTGGCACGATCTTGGCTCACTGCAACCTCGGCCTCCAGGT
TCAAGTTATTCTCCTGCTTCAGCCTCCTGAGTAGCTGGGATTATAGGCACA
[C/T]GCCCCCATGCCTGACTAATTTTTGTATTTTAGTAGAGACGGGGTTTC
ACCATGTCAGGCTGGTCTTGAACCTCCTGACCTCAGGTTATCCACCCGCCTT
GGCCCCCTCAAAGTGTTGGAATTACAGGTGTGAGCCACCGTGCCTGGCCTG
TTCACATGTATAAAACACAGTTTAATGTCCTATTCCCAGCCAATGAGC

FIG. 8.23

SG13S39

TCAGGTTATCCACCCGCCTTGGCCCCCTCAAAGTGTTGGAATTACAG
GTGTGAGCCACCGTGCCTGGCCTGTTACATGTATAAAACACAGTTTAAT
GTCCTATTCCCAGCCAATGAGCATGGCTAGAGCAGCCTTGGTCAAAGTTT
GGTTTTTGGAGAAAAATCCTTGTTAGCTGACCTAAGATTCTCTTTGTGAG
T[G/T]TAAGTAAGCACAGGTTGCAGAGAGGAGAAGGGTCTCTGGAGAGGT
GTAATTTTCTAAATGGATTACAAGTTCATGGACTTTTAACAGGTGTTACAG
GGGATAACAAGTTCTTTATAGACAGACTTTTGAGGACGTTTAAGGGTATTC
TGATTCTTGGTTTTCTAAGAGGGGAATGTATTATTAACTACAGACACCC

SG13S142

AAAATCCAGAATAATAATAATTTGTCAATAGGAAAGACATTTCCAC
TGGGGGTAAAGAAGGAAGACATTGGAACAATGATAGCCACCACTTATTGA
ATGCTTACTGTGAGCCAGGTGGCACTTCACCTTGTTTCATTCTCACAAACAG
TCTAGGGAAGTAATTACTAATGTCTCCATCCACCTCTTGTAGATGAGCAAA
[C/T]TGAGGCTCATTGAGGCTAGGAAATGCACCCACACTCACATAGCCCAT
AAGAGGCAGCCATGGCATTGGGCCCAGACCATGTGAACTTCAAAGACTAC
ACGAGCAGCCACTGGGCAGCTGTCATGGCTAAAGCCACTTGAATTCAGCC
CAGCAGCAACCCCTCTCCAGGAGGGGCACATAAGCTTGCAGCTTTGGGT

SG13S143

ATAATAATAATTTGTCAATAGGAAAGACATTTCCACTGGGGGTAA
GAAGGAAGACATTGGAACAATGATAGCCACCACTTATTGAATGCTTACTG
TGAGCCAGGTGGCACTTCACCTTGTTTCATTCTCACAAACAGTCTAGGGAAG
TAATTACTAATGTCTCCATCCACCTCTTGTAGATGAGCAAACCTGAGGCTCA
[C/T]TGAGGCTAGGAAATGCACCCACACTCACATAGCCCATAGAGGGCAG
CCATGGCATTGGGCCCAGACCATGTGAACTTCAAAGACTACACGAGCAGC
CACTGGGCAGCTGTCATGGCTAAAGCCACTTGAATTCAGCCCAGCAGCAA
CCCCCTCTCCAGGAGGGGCACATAAGCTTGCAGCTTTGGGTAGAAGCTGC
A

SG13S144

GCACTTGAAGTCCTGGATGGCGAGAGGGACTGGCTTGAGCCAGAG
CCAGGAACAAGGCTCTGAGAATATTCTGGAAATCCACAGGAGGAACCCAT
TTTCTTACAGCTGGGAGAATTTCACTCACTCCAGGCTGACCATGTTTTAT
TAGGAACGAAGGTGACTTGAACATAAGTCAGGAATGGTTGAATACGGAC
CC[A/G]ATGTCAAATCACTAGGCAGTTCACATTTCTAATGAGCAAATCCCT
TAGACAATTAAGAATTTTTTCTTTTGCATAACCCAGACAAAATCGCTAC
TAAAAACAAACCAAAGACCCGAAACATGAGAAAGAGAAGGAAGCAGG
GGAAATCTTTGGTACTAATAAGTTTTTAAACAATAAGAGCACCAGATATTT
TA

SG13S145

ATGAGCAAATCCCTTAGACAATTAAGAATTTTTTCTTTTGCATAA
CCCAGACAAAATCGCTACTTAAAAACAAACCAAAGACCCGAAACATGAG
AAAGAGAAGGAAGCAGGGGAAATCTTTGGTACTAATAAGTTTTTAAACAA
TAAGAGCACCAGATATTTACCCCATCAGACACAGAATGTTATTCGAATA
AC[C/G]AAAAAAGGAATTTTTTCTCTAAGTTTCTTGAACCTGGAAAATGAAT
CATATTTTCTCAGTCCTGAGGCTGCAATTTTGTGCCTCTAGTAACATATAA
GAATAGATGTGATGCCAGTGCCAGTAGCTGCTGCAATTGTTACTTGGGG
ACCTGTTTATTCTAAGCACTTCACCCAGTGATAAATTTGTAGGGGCCT

SG13S146

CCGTGTCCATTAGATCAGTGGAATTTCTGGGATTCAGAGCACTTTG
CAAGGTCAGCAGGGGTCTGCTCTTTCTGTCCTGTTCTCTGGTTTTTGGTTGTG

FIG. 8.24

CCTGGATTCCAGGGTAGGTTTCTCATCTGTTACCTTCATAGACTTCTCCAG
AAAAGGATCTTTTGACCATCAGAGGACCACGAAGATTCCATTGGTGAGG[
C/T]GCAGATAACCTGATCTCTCTGGGTTCTCTGCAGGGCACAGATGAAGG
GCTGGCCATTCCCAAGTTCTCAGTGGTACCCTGAGGCATGAGACCCTAA
TGGTTTGCATGAGCAGTTTGAAAATTGCATCTTTGTTTTTACCTATATAATC
ACATGAAACCCGTGGTTCTCAAACGTCAGCAGGCATCAGCATCACATG
SG13S26

TCAGTGGTACCCTGAGGCATGAGACCCTAATGGTTTGCATGAGCA
GTTTGAAAATTGCATCTTTGTTTTTACCTATATAATCACATGAAACCCGTG
GTTCTCAAACGTCAGCAGGCATCAGCATCACATGGAGGGCTTGTTAAAC
AGATTTCTGGGCCCCAACACAGAGTTTTAAATTCTGAAGGCCTGAGGTGG
G[C/T]GTGAACATTTGCATTTCTAACATGTTCTCGATGCTGCTGCCGCCTCT
GGTCCCGAGAGCATGCCTGGGAGAACTGCCACCTTCGACCATGGACTGTGA
GAATTCACATGGACCTCAGAATTATAATCAGTCTCTCAGTTTTACAGATAA
GGAAACTAAATCCAGAGAGATTGTTTTGCCAATGGTGAACAGCTGGTTA
SG13S27

ATGGTTTGCATGAGCAGTTTGAAAATTGCATCTTTGTTTTTACCTAT
ATAATCACATGAAACCCGTGGTTCTCAAACGTCAGCAGGCATCAGCATCA
CATGGAGGGCTTGTTAAACAGATTTCTGGGCCCCAACACAGAGTTTTAA
ATTCTGAAGGCCTGAGGTGGGTGTGAACATTTGCATTTCTAACATGTTCTC
[A/G]ATGCTGCTGCCGCCTCTGGTCCCGAGAGCATGCCTGGGAGAACTGCCA
CCTTCGACCATGGACTGTGAGAATTCACATGGACCTCAGAATTATAATCA
GTCTCTCAGTTTTACAGATAAGGAACTAAATCCAGAGAGATTGTTTTGCC
AATGGTGAACAGCTGGTTAAAGTCAGGATGGAGACTTTAATCCTAGTCA
SG13S147

GAGCAGTTTGAAAATTGCATCTTTGTTTTTACCTATATAATCACATG
AAACCCGTGGTTCTCAAACGTCAGCAGGCATCAGCATCACATGGAGGGCT
TGTTAAACAGATTTCTGGGCCCCAACACAGAGTTTTAAATTCTGAAGGC
CTGAGGTGGGTGTGAACATTTGCATTTCTAACATGTTCTCGATGCTGCTGC[
C/T]GCCTCTGGTCCCGAGAGCATGCCTGGGAGAACTGCCACCTTCGACCAT
GGACTGTGAGAATTCACATGGACCTCAGAATTATAATCAGTCTCTCAGTTT
TACAGATAAGGAACTAAATCCAGAGAGATTGTTTTGCCAATGGTGAACA
GCTGGTTAAAGTCAGGATGGAGACTTTAATCCTAGTCAAGTGACCTTTC
SG13S28

AGTTTGAAAATTGCATCTTTGTTTTTACCTATATAATCACATGAAAC
CCGTGGTTCTCAAACGTCAGCAGGCATCAGCATCACATGGAGGGCTTGTT
AAAACAGATTTCTGGGCCCCAACACAGAGTTTTAAATTCTGAAGGCCTGA
GGTGGGTGTGAACATTTGCATTTCTAACATGTTCTCGATGCTGCTGCCGCC
[G/T]CTGGTCCCGAGAGCATGCCTGGGAGAACTGCCACCTTCGACCATGGAC
TGTGAGAATTCACATGGACCTCAGAATTATAATCAGTCTCTCAGTTTTACA
GATAAGGAACTAAATCCAGAGAGATTGTTTTGCCAATGGTGAACAGCTG
GTAAAGTCAGGATGGAGACTTTAATCCTAGTCAAGTGACCTTTCCTCT
SG13S148

CATCTTTGTTTTTACCTATATAATCACATGAAACCCGTGGTTCTCAA
ACGTCAGCAGGCATCAGCATCACATGGAGGGCTTGTTAAACAGATTTCT
GGGCCCCAACACAGAGTTTTAAATTCTGAAGGCCTGAGGTGGGTGTGAAC
ATTTGCATTTCTAACATGTTCTCGATGCTGCTGCCGCCTCTGGTCCCGAGA[
G/T]CATGCCTGGGAGAACTGCCACCTTCGACCATGGACTGTGAGAATTCAC
ATGGACCTCAGAATTATAATCAGTCTCTCAGTTTTACAGATAAGGAACT

FIG. 8.25

AAATCCAGAGAGATTGTTTTGCCAATGGTGAACAGCTGGTTAAAGTCAGG
ATGGAGACTTTAATCCTAGTCAAGTGACCTTTCCTCTGTATTTATTTCCC
SG13S98

ATTTCTGACATCCTGAACCATAGTAAAAGGGTGTTTTTTTGTTTTTTT
GAGACAGAGTCTTGCTCTGTTGCCTGGGCTGGAGTGCAGTGGTGTGATCTT
GGCTCGCTGCAACCTCCGCCTCCCAGGTTCAAGTGATTCTCCTGCCTCAGC
CTCCTGAGTAGCTGGGATTACAGGTGCTTGCCACCACACCTGGCTATTT[G/
T]TTGTGTTTTTAGTAGAGACAGGGTTTCACCATGTTGGCCAGGCTGGTCTT
GAACTCCTGACCTTGTGATCTGCCTGCCTCAGCCTCCCAAATTGCTGGGAT
TACAAGGCGTGTTGTTTTAAGCCACTCAGTTTGTGGCCACTTGTACAGCA
GCAAGAGGAACTCATACAGTTATCATGTGAACTCACAGGAATAT
SG13S149

GATCTGCCTGCCTCAGCCTCCCAAATTGCTGGGATTACAAGGCGTG
TTGTTTTAAGCCACTCAGTTTGTGGCCACTTGTACAGCAGCAAGAGGAA
ACTCATACAGTTATCATGTGAACTCACAGGAATATGGTGAGTTAAAAAGA
GAGGAAGGGTGCAAAACATCCACGGTAGAGTGAGAACTCTCCAGGGAGT
GAG[A/G]ACTGTGCCCAGCATAACAGTGATCACCTCTTAGTAAGCTAAGTT
TCTGAGCACCAGCTTTTTTTGAGTTGACTTTGTTGTCTTTAACATTTGAAGAT
CACCTTCTTTGCTCAGCCTGGCTTGACAGACCTGGGCTGATTTGTGGATCT
GATAGAAAAGTTTCCTTAGTTGGGCTCTTCTCCCCGACCACCCCATGCC
SG13S29

TGCCTCAGCCTCCCAAATTGCTGGGATTACAAGGCGTGTTGTTTTA
AGCCACTCAGTTTGTGGCCACTTGTACAGCAGCAAGAGGAACTCATAC
AGTTATCATGTGAACTCACAGGAATATGGTGAGTTAAAAAGAGAGGAAG
GGTGCAAAACATCCACGGTAGAGTGAGAACTCTCCAGGGAGTGAGGACT
GTGC[A/C]CAGCATAACAGTGATCACCTCTTAGTAAGCTAAGTTTCTGAGC
ACCAGCTTTTTTTGAGTTGACTTTGTTGTCTTTAACATTTGAAGATCACCTT
CTTTGCTCAGCCTGGCTTGACAGACCTGGGCTGATTTGTGGATCTGATAGAA
AAGTTTCCTTAGTTGGGCTCTTCTCCCCGACCACCCCATGCCAGTGTTGGC
SG13S89

GCTACTTTGCAGCCAAGGTAACCTCAGACTTCCCTTTGTTTCAATTCTCC
TTCTATAAAGTGCACTCTCAAGGAGGTTCAAAGGGCAGGCTTTTTGTTGAA
AGGACTTTGCCTGACCTCTGGCTCCCCTCTGTGAAGCCCTGGAGAGGTGA
GAGCCCTCGGGAGGCCGTGTTTCAGGCATGCTCTGCACCCGTGCAGAGCG
C[A/G]TGTGATAATGCATTGCTAATGCTTGCTCCCTGGTGGCTGGCTGAGA
GCTGCTGTGCTGACAAGGGTGGTTTAAGGCTAAATGTGACTCAGAATCCT
TAAGCAGTGTTAGTTCAGATACAAGGGCATTATAAATGAGAGTGCCTGAG
GGATCTATTTTGGGACCGCTGTCAGTTGGCTCTTCTGCTAATAAGCTTCCA
SG13S96

ACAGTTATCAGCAGCCCACAGGCTTGACTTGAGCAAGTTGGAAAG
ACAAATCAACTTCCAGAGTTGATTTAACATTGAGTGGAATCAGTCATAC
TTTTGGTCCCCTTTTCGGGGCCACGCCTGGCACTGTGCCTGGTGGCAGATCG
GCATGAACTGGCCAGCTTCTGTGGCCCTGGAGGGCACAGGCAGAAAGGCC
AC[A/G]CTCAGTCCCATGATGAACTGTTTAAGACTTATTGTTGTCTCCCCGC
TCTGTAAAGTAGATAGAGTGGATTTTATGTCCCTTATTACCTTTCAGGATA
CTTTGACTCAGGGAGATAAAGTAACTTGGGTACAGCTACTCAGCTGGTGA
AGAACACAGGCAGAAATGAGTGCCTGGGTCTTTTGAAGTTAAATTTCTGGAT
SG13S150

CTGTGCCTGGTGGCAGATCGGCATGAACTGGCCAGCTTCTGTGGCC
CTGGAGGGCACAGGCAGAAAGGCCACACTCAGTCCCATGATGAACTGTTT

FIG. 8.26

AAGACTTATTGTTGTCTCCCCGCTCTGTAAAGTAGATAGAGTGGATTTTAT
GTCCCTTATTACCTTTCAGGATACTTTGACTCAGGGAGATAAAGTAACTTG
[C/G]GTACAGCTACTCAGCTGGTGAAGAACACAGGCAGAATGAGTGCCTG
GGTCTTTTGACTTAAAATTCTGGATTTTTCACAAAGATCCTCTTACTTTATT
CATTTACATAATAAATATATATTGAAGAGCTACTCTGTGCCAAGCCCTGTG
CCTAGATATACAGTGATAAATAAAGAGTAGCTTCTAGAGGTCACCTGG
SG13S401

AAGTTCAGTGATAGAGAGCAGAGGTTGAGGCGGCAGCAGAAACCAC
TTAAGGGACACCACGTGGCACTCCTTCTGTGCTGAGAAGGCTGTCAGTAA
GCTCACCATTATTTTCTATTTTCTCTCCTGAGTTAAATAGGAAACATGTCT
CGCATTACTTGAAAAATCAAGTCAAACATGCTCTTACTAGGAGTTATGGT
[C/T]CTTTTATGTCTTAGATGATGCTTGATCTAGATGAATGCGGACTTGCT
GTAGCTAGATAAAATACAATGGGAGTTTGAAGGTGTTTCGTAGCCCTGGAA
ATAGGTATTTCTGTCAAAACAAGCTTTGTCATTGCCAGCAGACAAAAGC
ATCAGTAACCTTGTTGATAATCGTCATTTCTTAGGAATAAAGTAGACT
SG13S151

GTATTTCTGTCAAAACAAGCTTTGTCATTGCCAGCAGACAAAAGC
ATCAGTAACCTTGTTGATAATCGTCATTTCTTAGGAATAAAGTAGACTGT
AGAATTTTTTTTAGCAGAAAGGAAACCCAAAGATAATTCTAGTGCAAATC
CCTCACTTTATAGAGCAGAAGCTCAAGTCCCAGAGGAACAAGTGGCTTGA
A[C/T]GAACATCAGAATTTTAGGGGCTGGATTTGTACCCTCCTGGTGCCAG
CAGCCCACTTCCCTGCAGGAGGCACTCACCTTCCTTGACAGGGGTATGA
GTGTGGCCATTTTCCACCCATAATCTCTGTTAGCTCATGTTCAATTGGGTT
CCCATTGAAAGAAAAATGGACCAGTAAGTTGGAGCAGAATCATTAGATG
SG13S30

AGCTTTGTCATTGCCAGCAGACAAAAGCATCAGTAACCTTGTTGA
TAATCGTCATTTCTTAGGAATAAAGTAGACTGTAGAATTTTTTTTAGCAGA
AAGGAAACCCAAAGATAATTCTAGTGCAAATCCCTCACTTTATAGAGCAG
AAGCTCAAGTCCCAGAGGAACAAGTGGCTTGAACGAACATCAGAATTTTA
G[G/T]GGCTGGATTTGTACCCTCCTGGTGCCAGCAGCCCACTTCCCTGCAG
GAGGCACTCACCTTCCTTGACAGGGGTATGAGTGTGGCCATTTTCCACCC
ATAATCTCTGTTAGCTCATGTTCAATTGGGTTCCCATTTGAAAGAAAAATGG
ACCAGTAAGTTGGAGCAGAATCATTAGATGGTATAACATAAGGAAAAA
SG13S31

TGTTTAAATTGCTTTTATATCTGTAGCTCTAGATAAACACTAGTTCCA
GCTTAGTTAACTCCCAGCTCCAAGCCTTCAGGACTTCATAGAGTTATTGGG
GTGCTGCTCTTGGCAGTTTCCCAAAAAGCTAGAATGCAGAGGGAATCTCC
TTCCCAAAAAGCTAGAATGCAGAGGGAATCTCCTTCCCAAAAAGGCTAGAA
[C/T]GCAGAGGGAATCTCCTTCCCAAAAAGCTAGAATGCAGAGGGAATCT
CCTTCCCAAAAAGGCTAGAACGCAGAGGGAATCTCCTTCCCAAAAAGGCTAG
AACGCAGAGGGAATCTCCTTCCCAAAAAGGCTAGAATGCAGAGGGAATGT
CCTTCTCTTCTAAATGGTAGCTGTTAGTTCAAGAAAGGTTAAACATTGTGC
T
SG13S152

GCTGCGTTTGCTGGACTGATGTACTTGTTTGTGAGGCAAAAAGTACT
TTGTCGGTTACCTAGGAGAGAGAACGCAGAGGTAGGTAACTGGGACTACT
AAAGAACTGTGGAGCGATTCTGATTTTGTAGCAGGAAGAGTGACAATTC
AAAACAGTATTTGACTAGATTCACGGCTCCGTAGCATCCCCTTGGGTGGG
AG[C/G]GGGAAGGCTGACTAGGACCTCTGATTCTTCTTCCCTGAGCTTTG
AAGGCTCTGAAAATACAGCTGGGGGGACTTGCCAGTTTTCTTATTAAGC

FIG. 8.27

AATTCCTCCGCATGGTGCTGGCTTTCAAAGGGTGCTTCAGTGCTGTTTGCT
GCACGTGCCTTGCAGCCCCACACCCTGCACTCCCGCCCTGCAGAGTCTGG
C

SG13S402

GAGGCCAAAAGTACTTTGTCTGGTTACCTAGGAGAGAGAACGCAGAG
GTAGGTAAGTGGGACTACTAAAGAACTGTGGAGCGATTTCCTGATTTTTGA
GCAGGAAGAGTGACAATTCAAAACAGTATTTGACTAGATTCACGGCTCCG
TAGCATCCCCCTTGGGTGGGAGGGGGAAGGCTGACTAGGACCTCTGATTCT
TCT[C/T]TCCCTGAGCTTTGAAGGCTCTGAAAATACAGCTGGGGGGGACTTG
CCCAGTTTTCTTATTAAGCAATTCCTCCGCATGGTGCTGGCTTTCAAAGGG
TGCTTCAGTGCTGTTTGCTGCACGTGCCTTGCAGCCCCACACCCTGCACTC
CCGCCCTGCAGAGTCTGGCGCTGGAATGACATTTTAGGTCTGGGTTCCTCA
G

SG13S403

TATCTTTCAGGGACCAGAAGAAAGAATGTTGGGAAAATAAGATGC
AGTAAGATGCAGACATGACAGCAGGGTGACGCGGCTCACGCCTATAATCC
CAGCACTTTGGGAGGCTGAGGTGGGTGGATCACCTGAGGTCAGGAGTTTG
AGACCAGCCTGGCCAACATGGTGAAACCCCGTCTCTACTAAAAAATATAC
AAA[A/G]CATTAGCCAGGCATGGTGGTGGGCGCCTGTAATCCCAGCTACTC
CATAGGCTGAGGCTGGAGAATCGCTTGAACCCAGGAGGCAGAGGTTGCA
GTGAGCCGAGATTGCGCCACTGCACTCCAGCCTGGGCAACAAAAGCAAA
ACTCCATCTCAAAAAAAAAAAAAAAAAAAAAAAAAAAGATGCAGACACG
AGACTG

SG13S153

TGGGCGCCTGTAATCCCAGCTACTCCATAGGCTGAGGCTGGAGAAT
CGCTTGAACCCAGGAGGCAGAGGTTGCAGTGAGCCGAGATTGCGCCACTG
CACTCCAGCCTGGGCAACAAAAGCAAACTCCATCTCAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAGATGCAGACACGAGACTGTGAACTGACTAGCAT
CACC[A/T]TTGCATTGTTTATAGATGTTGCCAGACAGAAAGCCCCAAAGCA
GCACAGTACCTTCCTGACATCTGGACTAGGAAATCTAGATTTTAGTAAAA
TACATGCTAATACTTACAGAAGAAATGTCGGCGTTAGAGTATGCCGTCAG
TTCCTTAGAGATTGCAATTCCTAATGCACTAGTATGGTTTCAGGTGCCAGG
AAC

SG13S97

ACTCCATCTCAAAAAAAAAAAAAAAAAAAAAAAAAAAGATGCAG
ACACGAGACTGTGAACTGACTAGCATCACCATTGCATTGTTTATAGATG
TTGCCAGACAGAAAGCCCCAAAGCAGCACAGTACCTTCCTGACATCTGGA
CTAGGAAATCTAGATTTTAGTAAAATACATGCTAATACTTACAGAAGAAA
TGTC[A/G]GCGTTAGAGTATGCCGTCAGTTCCTTAGAGATTGCAATTCCTA
ATGCACTAGTATGGTTTCAGGTGCCAGGAACACGTTCTGTGAGGCTGCTG
CCCCAGGTGCTGACCCAGCCTTCCACACCATTTTCCTTCCTTGTGTTTAC
AGCCGCTCTGTCTTTTACAATAGCACCCCTCTCTAGTGGCTAATGGGCTCT
AT

SG13S154

AAAAAAAAAAAAAAAAAAAAAAAAAAGATGCAGACACGAGACTGTGAA
ACTGACTAGCATCACCATTGCATTGTTTATAGATGTTGCCAGACAGAAAG
CCCCAAAGCAGCACAGTACCTTCCTGACATCTGGACTAGGAAATCTAGAT
TTTAGTAAAATACATGCTAATACTTACAGAAGAAATGTCGGCGTTAGAGT
ATGC[C/T]GTCAGTTCCTTAGAGATTGCAATTCCTAATGCACTAGTATGGTT
TCAGGTGCCAGGAACACGTTCTGTGAGGCTGCTGCCCCAGGTGCTGACCC

FIG. 8.28

CAGCCTTCCACACCATTTTCCTTCCTTGTGTTACAGCCGCTCTGTCTTTTA
CAATAGCACCCCTCTCTAGTGGCTAATGGGCTCTATGATTAGATAGCATCC
SG13S40

TTTCAGGTGCCAGGAACACGTTCTGTGAGGCTGCTGCCCCAGGTGC
TGACCCCAGCCTTCCACACCATTTTCCTTCCTTGTGTTACAGCCGCTCTGT
CTTTTACAATAGCACCCCTCTCTAGTGGCTAATGGGCTCTATGATTAGATA
GCATCCTTCAGTAGTGATAAAGGCAGTGACATCCTAGGGAGGTCAGCGG[
G/T]TGAAAGCGCTATATCTGGAAAACCTGAGAGCCTGTGAAGCTCAAGGA
CTTGACGGGGTTAGACCGTGAGCCGGGCTGCAGCTGGAAAAAGAATGACT
GTTCTTTACGAGATCCTTCCCTGTGCCATCTCTTTCTTCATTCCCTCTCTAG
TGGCATTCTTATTTATCCTCTAAAACCAATTCCATTATCTCTCCTA
SG13S155

GAGGGTCTTCTCTTTTGCCTGGCTCCCTATGCAGCCCTATCTTACCC
CCTGCAAAGTCCCAGGGATGTGGCTCAGTCACTGCTCCTCTCTTCATCTGT
CACCATTGCTTGAGATCCTACAGCTGCTTTAATTCCGAGACCATCTGCAG
AACATGACAAAATTTGTCCACCTACCCACATGTCTTTTAACTTTAAAG[A/
G]CTTTACTAACTGATTCTTATTAGGGAATGAACAGAGGTGGCAAAAATAA
ACAATAGGAGATTGATTTACAAGAAATCTTTAAAATAGTAGATTTCTTCG
GACCTCATTGAAATATAAATGGCCTGCCTTCTTGTGTCCCTCCCTGGTCTC
CCTCTTTAGGTGATAAGAAGAAGATCCTGCCAGCCCCATAACCCGCC
SG13S156

TTAAAATAGTAGATTTCTTCGGACCTCATTGAAATATAAATGGCCT
GCCTTCTTGTGTCCCTCCCTGGTCTCCCTCTTTAGGTGATAAGAAGAAGAT
CCTGCCAGCCCCATAACCCGCCATCTGCGCGGGTTCTAGACCCCTTCTCC
TCCCTCTGGCCGTGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTT[A/
C]CAGAGACCAAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGCTT
AACACAACCACTCTGAGCAGCTGTCATAAGTAGAAGTAATAGATACTAGA
AGAAATGTCTAAGCCTAATCTAGACCAAAATACGGCCTGATATAGATGCA
AGCCAGAGGGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCG
SG13S157

CTGGTCTCCCTCTTTAGGTGATAAGAAGAAGATCCTGCCAGCCCCA
TAACCCGCCATCTGCGCGGGTTCTAGACCCCTTCTCCTCCCTCTGGCCG
TGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTTCCAGAGACCAAACC
TGGCCTCGGAATCCTTCTTAACACAGATACTGCTTAACACAACCACTCTG[
A/G]GCAGCTGTCATAAGTAGAAGTAATAGATACTAGAAGAAATGTCTAAG
CCTAATCTAGACCAAAATACGGCCTGATATAGATGCAAGCCAGAGGGGCT
TTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAGAAGCTACTTG
CTGAGATCTTCTTCAGTTGGGCCCATCTCCTCCCCAGGCCTCTCTTCTG
SG13S158

CCATAACCCGCCATCTGCGCGGGTTCTAGACCCCTTCTCCTCCCT
CTGGCCGTGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTTCCAGAGA
CCAAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGCTTAACACAAC
CACTCTGAGCAGCTGTCATAAGTAGAAGTAATAGATACTAGAAGAAATGT
[A/C]TAAGCCTAATCTAGACCAAAATACGGCCTGATATAGATGCAAGCCA
GAGGGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAGA
AGCTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCCCCAGGCCTC
TCTTCTGTTCCCTGGGCTATGTCACACTTGGACTCTGCAGACACCTAATGC
SG13S159

TGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTTCCAGAGACC
AAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGCTTAACACAACCA

FIG. 8.29

CTCTGAGCAGCTGTCATAAGTAGAAGTAATAGATACTAGAAGAAATGTCT
AAGCCTAATCTAGACCAAAATACGGCCTGATATAGATGCAAGCCAGAGG
GGC[G/T]TTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAGAAG
CTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCCCCAGGCCTCTCT
TCTGTTCTGGGCTATGTCACACTTGGACTCTGCAGACACCTAATGCTCTT
GGGACCTGCTTTAGTTCTTGACCTCACCAACCGAGGAGGAATTGCTAGAT
SG13S160

CAGAGACCAAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGC
TTAACACAACCACTCTGAGCAGCTGTCATAAGTAGAAGTAATAGATACTA
GAAGAAATGTCTAAGCCTAATCTAGACCAAAATACGGCCTGATATAGATG
CAAGCCAGAGGGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCC
GT[C/T]TAGAAGCTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCC
CCAGGCCTCTCTTCTGTTCCCTGGGCTATGTCACACTTGGACTCTGCAGACA
CCTAATGCTCTTGGGACCTGCTTTAGTTCTTGACCTCACCAACCGAGGAGG
AATTGCTAGATGAGATCCTTCCCCCGGAATTTCTCTCTTGAACCCCA
SG13S32

GGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAG
AAGCTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCCCCAGGCCT
CTCTTCTGTTCCCTGGGCTATGTCACACTTGGACTCTGCAGACACCTAATGC
TCTTGGGACCTGCTTTAGTTCTTGACCTCACCAACCGAGGAGGAATTGCT[
A/C]GATGAGATCCTTCCCCCGGAATTTCTCTCTTGAACCCCAAGATGGTCCG
TTGCCCTTTCCAGAAGTTGCTCCAGCCCTGTCCGCTTAGGAAGTTCAGTG
TCATCCTTGATCCAGTGGGTAGGGAAGACATTCCATAATGAATGCCCCAG
TCTGAGCTTCTTCCCTCAGGCTTCAGGCTGCCCTGCGAGGATTTTGCA
SG13S161

GTAGCTGAGACTACAGGTGTGCACTACCACACCCAGCTAATTTTTT
GTATTTTATAGTAGAGATAGGGTTTAGCTATGTTGGCCAGGCTGGTCTCGAA
CTGCTGAACTCAAGCAATCTGCCATCCCCGGCCTCCCCAAAGTACTGGGAG
TATAGGCATAAGCCACCCATGATGCCCAGCCTGAATCTTGGTTTCTTCCCC
[A/G]TTCATTTAAGCTATTACCTGGGCCTGAACTCAATGGCACCTGGCACC
AACTGGCAACTGACTCTTGGTCTTTTATTACCTACCTTCCCTAGCAGGCAC
TGGGTTGCTCCCTCTTCCCTATCCCATGGAGTCCTGTCTCTGTTGGGGCTCC
TACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAATGGTGGGTG
SG13S162

CCCGGCCTCCCCAAAGTACTGGGAGTATAGGCATAAGCCACCCATG
ATGCCCAGCCTGAATCTTGGTTTCTTCCCCATTCAATTAAGCTATTACCTG
GGCCTGAACTCAATGGCACCTGGCACCAACTGGCAACTGACTCTTGGTCT
TTTATTACCTACCTTCCCTAGCAGGCACTGGGTTGCTCCCTCTTCCCTATCCC
[A/G]TGGAGTCCTGTCCTCTGTTGGGGCTCCTACTGATCCTCTTGGCAATAT
GAAGTTCTCAGCTCAATGGTGGGTGGGCAATGACTGCCAACTCTTGAGGC
CAATGAACTCAGGTTACCCCACTCCTCCTCCTGAGTTGCTCACTCACT
CCTCATTCACTCAACATTGATTCAGTAGATATTTGCTACCTGCTCTGT
SG13S163

CCGGCCTCCCCAAAGTACTGGGAGTATAGGCATAAGCCACCCATGAT
GCCCAGCCTGAATCTTGGTTTCTTCCCCATTCAATTAAGCTATTACCTGGG
CCTGAACTCAATGGCACCTGGCACCAACTGGCAACTGACTCTTGGTCTTTT
ATTACCTACCTTCCCTAGCAGGCACTGGGTTGCTCCCTCTTCCCTATCCCA[C
/T]GGAGTCCTGTCTCTGTTGGGGCTCCTACTGATCCTCTTGGCAATATGA
AGTTCTCAGCTCAATGGTGGGTGGGCAATGACTGCCAACTCTTGAGGCCA

FIG. 8.30

ATGAACTCAGGTTACCCCACTCCTCCTCCTGAGTTGCTCACTCACTCC
TCATTCACCTCAACATTGATTAGTAGATATTTGCTACCTGCTCTGTG
SG13S164

GGCATAAGCCACCCATGATGCCAGCCTGAATCTTGGTTTCTTCCC
CATTCAATTAAAGCTATTACCTGGGCCTGAACTCAATGGCACCTGGCACCAA
CTGGCAACTGACTCTTGGTCTTTTATTACCTACCTTCCCTAGCAGGCACTG
GGTTGCTCCCTCTTCTATCCCATGGAGTCCTGTCCTCTGTTGGGGCTCC[C/
T]ACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAATGGTGGGTGGGCA
ATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTTACCCCACTCCTCCTC
CTCCTGAGTTGCTCACTCACTCCTCATTCACTCAACATTGATTAGTAGAT
ATTTGCTACCTGCTCTGTGCCAGGTACCAGGTCAGTTGCTGAAGGA
SG13S165

CCTGGCACCAACTGGCAACTGACTCTTGGTCTTTTATTACCTACCTT
CCCTAGCAGGCACTGGGTTGCTCCCTCTTCTATCCCATGGAGTCCTGTCC
TCTGTTGGGGCTCCTACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAA
TGGTGGGTGGGCAATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTT[A/
T]CCCCACTCCTCCTCCTGAGTTGCTCACTCACTCCTCATTCACTCAAC
ATTGATTAGTAGATATTTGCTACCTGCTCTGTGCCAGGTACCAGGTCAGT
TGCTGAAGGAGTAACAGTGAACATGACGGAGTCTTTGTCCCCAAGGAGAC
CCAAGGTGTCTCCTAGAGCCAGGGGCACATTGCAAGACCAAATATA
SG13S166

CTGGCAACTGACTCTTGGTCTTTTATTACCTACCTTCCCTAGCAGGC
ACTGGGTTGCTCCCTCTTCTATCCCATGGAGTCCTGTCCTCTGTTGGGGC
TCCTACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAATGGTGGGTGGG
CAATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTTACCCCACTCCT[C/
T]CTCCTCCTGAGTTGCTCACTCACTCCTCATTCACTCAACATTGATTAGT
AGATATTTGCTACCTGCTCTGTGCCAGGTACCAGGTCAGTTGCTGAAGGA
GTAACAGTGAACATGACGGAGTCTTTGTCCCCAAGGAGACCCAAGGTGTC
TCCTAGAGCCAGGGGCACATTGCAAGACCAAATATATTCAACTTACC
SG13S167

CCATGGAGTCCTGTCCTCTGTTGGGGCTCCTACTGATCCTCTTGGCA
ATATGAAGTTCTCAGCTCAATGGTGGGTGGGCAATGACTGCCAACTCTTG
AGGCCAATGAACTCAGGTTACCCCACTCCTCCTCCTGAGTTGCTCACT
CACTCCTCATTCACTCAACATTGATTAGTAGATATTTGCTACCTGCTCT[A/
G]TGCCAGGTACCAGGTCAGTTGCTGAAGGAGTAACAGTGAACATGACGG
AGTCTTTGTCCCCAAGGAGACCCAAGGTGTCTCCTAGAGCCAGGGGCACA
TTGCAAGACCAAATATATTCAACTTACCAAATAATCATAGACCTAGTTCT
CAAAAAGCAAGAAGACTGATTCCTCGTTGTCAATTTCTCCTCCTCAGCA
SG13S168

TTAGAGTCTGTGGGCCCCCTCCAAGTGTGGAGTATGGTGTACTTCA
CCAGAGTTTGAGGAGAAACATTCTTCTTTTGAAGGCCGGGGAGCATAGA
TGGATATCAAGGCTGCTGTTTCTAAAAGCGAAACCCACCAAACAACAGTA
TTAGAATCATCTGTGGTGCTTATTAAGATACAGATTCCTGGGCCCCATCC
C[A/C]GACTTATGAATCAGAATCTCTGCCAGAGGAAGCCTGAGAATTTGCA
TTCTCAGATGATTCTGCATTCTCAGATAACACATTCTTTAGGTGATTCTTAC
ACACACTGGAGTTTGGGAATCGCTGAAGGCTGTTCACTTCTCTTTTCTGAG
AAATGATTCAATTCATTTAGAAATATTTGCAGAGGTCCTTATTTATTG
SG13S33

TGGCCTCATTTCGTGTGATAAATCTGAGCCACCACGATATTTGACTTT
TCACAATTTAATTTATCTGAACCCTCTATTCTCTGGCTAAAAAATATCCCT

FIG. 8.31

TACTTGGACTTCTTTATTTTATTTTCAATTCCCTTACCAGCACTAGCAGGGG
ACTCTGTACTCATCTGCTGGCGCTGCCATAACAAAGCACTGCAGCCTG[G/T
]GGGGCTCAAACCACAGAATTTATTCTCTCACAGTCCTAGAGGCTAGAAGT
CCAAGATCAAAGTGTGGGCAGGGTCGGTTTCTCCTGCAGCCTCTCTCCTTG
GCTTATAGAGTGCCACCTTCTACCTGTGTCTTCACATCATCACCTCACTGA
GCATGTCTGTGTCCAAATCTCCCCTTCTTATAAGACCCCAGTCAT
SG13S41

TCTCCTTGGCTTATAGAGTGCCACCTTCTACCTGTGTCTTCACATCA
TCACCTCACTGAGCATGTCTGTGTCCAAATCTCCCCTTCTTATAAGACCCC
AGTCATACTGGATGAGGATCCACCCATATGAGTTCATTTTACCTTAATTAT
CTCTTTAAACACCCTGTCTCCAAATACAGTCCCATTCTGAGGAACTGAG[A/
G]GTAAAGATTCAACATATGAATTTTGGAAAGGGACCTAATTCAGCCCACA
ACACCCTCTTTTGGGATGTTTATTTTCCCCCTTAAGGAGCTAGTTAGGATG
TCTTATCTCATGAACATGACTGTGAACAGGAAAACAGGGAGAGAATGAA
GCTGGCCAAGGAACAGGGCTGGTGTGCTAGCAGTGCTTTTCTGATGT
SG13S169

CATTTTACCTTAATTATCTCTTTAAACACCCTGTCTCCAAATACAGT
CCCATTCTGAGGAACTGAGAGTAAAGATTCAACATATGAATTTTGGAAAGG
GACCTAATTCAGCCCACAACACCCTCTTTTGGGATGTTTATTTTCCCCCTT
AAGGAGCTAGTTAGGATGTCTTATCTCATGAACATGACTGTGAACAGGAA[
A/G]ACAGGGAGAGAATGAAGCTGGCCAAGGAACAGGGCTGGTGTGCTAGCT
AGCAGTGCTTTTCTGATGTGAGTGGGTCCACAGGGAGCTTGTTAAATG
CAGATTCTGATTCAATTAGGTTCCAGAGGGACCTGAGATTTCCCATTTCTGA
CAAGTTTCCAGTGTGGGGGCTGATGCTGCTGGTCCACGGACCATACTTTG
SG13S404

GGGAGAGAATGAAGCTGGCCAAGGAACAGGGCTGGTGTGCTAGCTAG
CAGTGCTTTTCTGATGTGAGTGGGTCCACAGGGAGCTTGTTAAATGCA
GATTCTGATTCAATTAGGTTCCAGAGGGACCTGAGATTTCCCATTTCTGACA
AGTTTCCAGTGTGGGGGCTGATGCTGCTGGTCCACGGACCATACTTTGAGT
A[G/T]CAAGGAGCTTGATACATAATGGCTGAGTGACTTTCAGACTCCTGCT
GTAGAAAAATTATGAGTTGGCTGGGCGTGGTGGCTCACGCCTGTAATCCC
AGCACTTTGGGAGGGCCGAGGTGGGCAGATCACCTGAGGTCAGGAGTTCTGA
GACCAGCCTGGCCAACATGGTGAACACCATCTCTACCAAAAATACAAAA
A
SG13S170

ACTTAAGCCCAGAAGACTGAGGTTGCAGTGAGCCGAGATTGCACC
ACTGCACTCCAGCTTGGGCTACAGAGTGAGACTCTATCTCAAAAACAAAG
AAACAAACAACAATAACAACAAAAACCAAGTCTCTCCCTCCACTCAA
AAATGCAAGGGCCTGTCTCCCATTTGCTGGGTGCCAGGTCTCATGAATGT
AGA[C/T]ATGAATTATTCCAGTCAGCCTCAGGAGAATAGAATGAGCCCTCA
GATGCCGAAGCACCTTTCAGATTCCACCGGTTTTATCGGCTCATTAAACT
TCACTTCTAACACAGTCCTGCATTACACACGTGTCTGTCGTTATGGGCAGC
TGCAGAGAGGGTCTTAATGGTCCTAATGCTCAGTGAGGATGCCCAATGGT
C
SG13S171

CTCAAAAACAAAGAAACAACAACAACAATAACAACAAAAACCA
AGTCTCTCCCTCCACTCAAAAATGCAAGGGCCTGTCTCCCATTTGCTGGGTG
CCCAGGTCTCATGAATGTAGATATGAATTATTCCAGTCAGCCTCAGGAGA
ATAGAATGAGCCCTCAGATGCCGAAGCACCTTTCAGATTCCACCGGTTTT
ATC[A/G]GCTCATTTAAACTTCACTTCTAACACAGTCCTGCATTACACACGT

FIG. 8.32

GTCTGTCGTTATGGGCAGCTGCAGAGAGGGTCTTAATGGTCCTAATGCTC
AGTGAGGATGCCCAATGGTCAACAGAACCTGCCATCTTCAGGCCATCAAG
GAGCTCTGGAGTTAAGGAAATCATGAGAGCACAGAGGGGGCGGGTACAGC
AGA

SG13S172

TGTAGATATGAATTATTCCAGTCAGCCTCAGGAGAATAGAATGAGC
CCTCAGATGCCGAAGCACCTTTCAGATTCCACCGGTTTTATCGGCTCATTT
AAACTTCACTTCTAACACAGTCCTGCATTACACACGTGTCTGTCGTTATGG
GCAGCTGCAGAGAGGGTCTTAATGGTCCTAATGCTCAGTGAGGATGCCCA
[A/G]TGGTCAACAGAACCTGCCATCTTCAGGCCATCAAGGAGCTCTGGAGT
TAAGGAAATCATGAGAGCACAGAGGGGGCGGGTACAGCAGAGCCCTCGTG
GTAATGGGTTTTGAGGTCTAGGCTCTCTTCACTTGGGTTTGAAATAAGTTC
AATGACTAGTAATAGCTGAGACACTTCTACCCTTCAAATGAAGTAAATGG

SG13S173

AGCACCTTTCAGATTCCACCGGTTTTATCGGCTCATTTAAACTTCAC
TTCTAACACAGTCCTGCATTACACACGTGTCTGTCGTTATGGGCAGCTGCA
GAGAGGGTCTTAATGGTCCTAATGCTCAGTGAGGATGCCCAATGGTCAAC
AGAACCTGCCATCTTCAGGCCATCAAGGAGCTCTGGAGTTAAGGAAATCA
[A/T]GAGAGCACAGAGGGGGCGGGTACAGCAGAGCCCTCGTGGTAATGGGT
TTTGAGGTCTAGGCTCTCTTCACTTGGGTTTGAAATAAGTTCAATGACTAG
TAATAGCTGAGACACTTCTACCCTTCAAATGAAGTAAATGGGAAAATGGA
GCATTGTTGAGTCCAGGGAGCTATAATTTAAACCCCATATATCTAAAAGG

SG13S42

CACACGTGTCTGTCGTTATGGGCAGCTGCAGAGAGGGTCTTAATGG
TCCTAATGCTCAGTGAGGATGCCCAATGGTCAACAGAACCTGCCATCTTC
AGGCCATCAAGGAGCTCTGGAGTTAAGGAAATCATGAGAGCACAGAGGG
GCGGGTACAGCAGAGCCCTCGTGGTAATGGGTTTTGAGGTCTAGGCTCTC
TTC[A/G]CTTGGGTTTTGAAATAAGTTCAATGACTAGTAATAGCTGAGACAC
TTCTACCCTTCAAATGAAGTAAATGGGAAAATGGAGCATTGTTGAGTCCA
GGGAGCTATAATTTAAACCCCATATATCTAAAAGGGGTAACATTTTTGTGT
GTGTGAAATTGGTGTCATTTCGCACTGCATCTACAGTTTTCTTTTTCTTCTC

SG13S194

ACATATTTGGGAAACGCATCATACTCTTCCTGTTCCCTCATGTCCGTT
GCTGGCATATTCAACTATTACCTCATCTTCTTTTTCCGGAAGTGACTTTGAA
AACTACATAAAGACGATCTCCACCACCATCTCCCCTCTACTTCTCATTTCCC
TAACTCTCTGCTGAATATGGGGTTGGTGTTCTCATCTAATCAATACCTA[C/
T]AAGTCATCATAATTCAGCTCTTGAGAGCATTCTGCTCTTCTTTAGATGGC
TGTAATCTATTGGCCATCTGGGCTTCACAGCTTGAGTTAACCTTGCTTTT
CCGGGAACAAAATGATGTCATGTCAGCTCCGCCCCTTGAACATGACCGTG
GCCCCAAATTTGCTATTCCCATGCATTTTGTTTGTTTCTTCACTTA

SG13S195

TGGTGTTCTCATCTAATCAATACCTACAAGTCATCATAATTCAGCTC
TTGAGAGCATTCTGCTCTTCTTTAGATGGCTGTAAATCTATTGGCCATCTG
GGCTTCACAGCTTGAGTTAACCTTGCTTTTCCGGGAACAAAATGATGTCAT
GTCAGCTCCGCCCCTTGAACATGACCGTGGCCCCAAATTTGCTATTCCC[A/
G]TGCATTTTGTTTGTCTTCACTTATCCTGTTCTCTGAAGATGTTTTGTGA
CCAGGTTTGTGTTTTCTTAAATAAAATGCAGAGACATGTTTTAAGCTGAT
AGTTGAGGGGTTTTGTTAATGGCTTTTGGGGGATTTATCTCTATACCCACA
AACGACTAGTTTGTTTTCTCAAACATAAATGATAATATTAATAA

FIG. 8.33

SG13S174

TTATCTCTATACCCACAAACGACTAGTTTGTTCCTCAAACCTAAAT
GATAATATTAATAACACATCCTGGCCAGGTGTGGTGGCTCATACCTGT
AATCCCAGCACTTTGGGAGGCCGAGGCAGGTGGATCACTTGAGGTCAGGA
ATTAAGACCAGCCTGGCCAATATGGTGAAAGCCTGTCTGTACTAAAAATA
C[A/G]AAAATTAGCCAGGTATGCTGGTGGATGCTTATAATCCCAGCTACTT
GGGAGGTTGAGGCAGGAGAATTGCTTGAACCCGGGAGGTAGAGGTTGCA
GTGAGCCAAGATCATGCCACTGCACTCCAGCTTGGGCAACAGAGTGAGAC
TCCATCTCAAATTAATAAAAAAATACACATCTGGCTTCTGGAAAAATTACTT
GA

SG13S34

GATCATGCCACTGCACTCCAGCTTGGGCAACAGAGTGAGACTCCAT
CTCAAATTAATAAAAAAATACACATCTGGCTTCTGGAAAAATTACTTGAAGA
TCTTTTATGACATCCATCCCTCTTCACACAGCCATGTGAATTAGGTTGGTA
TCTTCATATACTAGCATCGTGCCAGCACTTCCATGTTATACAGTTTAAAAA[
G/T]GTTCTGTAATTCCTGTGGGAACCTAAGATAATGCGAGGACCGTCAT
ACGTGCCCCCAAATATTGGCAAACCAATGAATAAATGAATGAATGAGTTT
ATGAATCGCTAACTGGCTGTATTTAATGAAGTATGTGTGTTGAGCCATTTC
CCACAGTGTGGACAGATTTGTCCCACAATATGGGCCTCTTCCCAAAGGC

SG13S175

AATTAATAAAAAAATACACATCTGGCTTCTGGAAAAATTACTTGAAGA
TCTTTTATGACATCCATCCCTCTTCACACAGCCATGTGAATTAGGTTGGTA
TCTTCATATACTAGCATCGTGCCAGCACTTCCATGTTATACAGTTTAAAA
TGTTCTGTAATTCCTGTGGGAACCTAAGATAATGCGAGGACCGTCATAC[
A/G]TGCCCCCAAATATTGGCAAACCAATGAATAAATGAATGAATGAGTTT
ATGAATCGCTAACTGGCTGTATTTAATGAAGTATGTGTGTTGAGCCATTTC
CCACAGTGTGGACAGATTTGTCCCACAATATGGGCCTCTTCCCAAAGGCC
CTACCACCTAATGCCATCACACTGGGGATTTGATTTCAACATGTGAATT

SG13S176

AGTTCATAGTGACAGTGATCCAGCCACTGTCATGACAGGTGCCACT
TGGCAGAAACAGCACAGCTTGGGAAGATGGCGGGGTGTAGTCAAGATTCC
AGGATCCCCAACAGAGAAGCCAGCTCTTATAGGGGAGCCATTTCATCAGGA
TTGAACTCTCAATCGAGCTGGACAGTAATAGGTGGGTCTGTGTTATCCCC
AG[A/G]TGAGTATCATGACAGTCACAATCCTAGGAAGGATGTGAAGCCTC
CCCCAGCTCTCCTCCAGTTGCCTGCTTGGGCAGCAGAGATGATGGAATGT
GGAGTCTGGCGTGGTCTGAGGCCTGAATCCATGTGCCTCATGTATGATGCT
CAGGCAAGAGGATCTCTCAATTCAAGGGAGAGGGCCTGAATGAGCCTTGC
TT

SG13S177

CTTGGCAGAAACAGCACAGCTTGGGAAGATGGCGGGGTGTAGTCAA
GATTCCAGGATCCCCAACAGAGAAGCCAGCTCTTATAGGGGAGCCATTCA
TCAGGATTGAACTCTCAATCGAGCTGGACAGTAATAGGTGGGTCTGTGTT
ATTCCCCAGATGAGTATCATGACAGTCACAATCCTAGGAAGGATGTGAAG
CCT[C/T]CCCCAGCTCTCCTCCAGTTGCCTGCTTGGGCAGCAGAGATGATG
GAATGTGGAGTCTGGCGTGGTCTGAGGCCTGAATCCATGTGCCTCATGTA
TGATGCTCAGGCAAGAGGATCTCTCAATTCAAGGGAGAGGGCCTGAATGA
GCCTTGCTTTCCAGGCCTGTCTGATGGTCCAGGCTGAAGCCCCCTCCTGGCT
TG

SG13S178

CTGGCGTGGTCTGAGGCCTGAATCCATGTGCCTCATGTATGATGCT

FIG. 8.34

CAGGCAAGAGGATCTCTCAATTCAAGGGAGAGGGCCTGAATGAGCCTTGC
TTTCCAGGCCTGTCTGATGGTCCAGGCTGAAGCCCCTCCTGGCTTGCACCTG
CCAGACCTCATCCAGCAGGAGCTCCTTGGCATTGACTGCTTCAGGATAGTT
[C/G]CTTCTGCTCTGAGTGCTCTCTAAAGAGCAGTGCTCTACCATCCAAGC
TGGGCTTTTCTTTTCTTCTTGCTGATAGGGAAGGCATGGGACATTGCAGGA
TGGAAGTGGCCCCCAGGCCTTCTCATGCCTGGGCTTGGTTTGAAGGTGG
TCAGGTGATCAATAATCCTGATTGGCCTGGCATTGAGGAGTTTTCCTGG
SG13S35

TGCTCTCTAAAGAGCAGTGCTCTACCATCCAAGCTGGGCTTTTCTTT
TCTTCTTGCTGATAGGGAAGGCATGGGACATTGCAGGATGGAAGTGGCCC
CCAGGCCTTCTCATGCCTGGGCTTGGTTTGAAGGTGGTCAGGTGATCAAT
AATCCTGATTGGCCTGGCATTGAGGAGTTTTCCTGGGATGTGGTCCTTTC[A
/G]GTTTTTTAAAAATTATTTTTATTGATACACATATTTGTAGGTATTTGTGG
GGTGCATGTGATACTTTATTATGTGTGTGGATTGTGTAATGATGAAGTCAG
GGCATTAGGGTCTTCATCACCTTGATTATCATTTCTATGTGTTGAGAACA
TTTCAAGTTCTCAGTTCAGCTATTTTGAAATAGACAGTCCATT
SG13S179

GATACTTTATTATGTGTGTGGATTGTGTAATGATGAAGTCAGGGCA
TTTAGGGTCTTCATCACCTTGATTATCATTTCTATGTGTTGAGAACATTTCA
AGTTCTCAGTTCAGCTATTTTGAAATAGACAGTCCATTTTGTAGCTACA
GTCACCCAACCCGGCTGTCAGACATTGGAACCTACTCCTATTGAACTGT[A/
G]TATTTGTACCCATTACCAAACCTCTCTTTGGGCTTTCAGTTTTACAACCTG
GGATGATCCTGGGAAAACATAAAGTAAATCAGACACCCGACGTGTGAGCTA
GGTTATAATATGCCCAGTGGACCCTGGGGACATCTTAGCTTTCAGAGGTC
ATGCTGTCCAAGCTGACTGTGGGGCTTCCAGAAGGTGGGGAGAGGAA
SG13S180

TATGTGTGTGGATTGTGTAATGATGAAGTCAGGGCATTTAGGGTCT
TCATCACCTTGATTATCATTTCTATGTGTTGAGAACATTTCAAGTTCTCAGT
TCCAGCTATTTTGAAATAGACAGTCCATTTTGTAGCTACAGTCACCCAAC
CCGGCTGTCAGACATTGGAACCTACTCCTATTGAACTGTGTATTTGTAC[C/
T]CATTCACCAAACCTCTCTTTGGGCTTTCAGTTTTACAACCTGGGATGATCCT
GGGAAAACATAAAGTAAATCAGACACCCGACGTGTGAGCTAGGTTATAATA
TGCCAGTGGACCCTGGGGACATCTTAGCTTTCAGAGGTCATGCTGTCCA
AGCTGACTGTGGGGCTTCCAGAAGGTGGGGAGAGGAAATGATGCAAT
SG13S181

TGGGAAAACATAAAGTAAATCAGACACCCGACGTGTGAGCTAGGTT
ATAATATGCCCAGTGGACCCTGGGGACATCTTAGCTTTCAGAGGTCATGC
TGTCCAAGCTGACTGTGGGGCTTCCAGAAGGTGGGGAGAGGAAATGATGC
AATGGCCCATCAGAGGCACTACTTGGGGCCTGGGGCCAGAGTGCATGTCT
AAG[C/G]CATTAAAGGGGAGGGGAGAGCAGCCTTCATAATTATGAAGAGGA
GTCTCAGGTGCACAGCTTCTGATGAGGGACAGCTTCTAATTGAAGACAGC
ATTGTGTAATGCTCAAACCTCCCTGTCTTCAGAGTGCCTGCTGTATCCCACC
ATCAGTTCTGTGACTTCTCCCTAAGCCTCAATTTTGCATGTGTTACATTGG
GA
SG13S182

CCTGCATAGCAAATTCTTGCAAATGTAGGGACTCAAAACAATATAA
ATTTATTATCTGACAGTTTTTCTGGGTCAGAGGTCTTACTAGGCTGTAATC
AGAGGGCAACCAAAGCTGTGATCTCAGCTGAAGCTCAGGATTCTCTTCCA
AGCTCACTGGTTGTTGGCAGAATTCAGTTCTTTCCAGTTGGAAGACTAAAG
[C/T]CTACAGTCTTCAGTCTCTAGAAGCCTTTTCTCTGGCACAGGTTTCTCT

FIG. 8.35

ACAACATGGCCATTTATGTCTTTAAGGCCAATAGGAGAACATGATTAGCA
TATTTTTTTTAAAGTGAACCTTTAGACCTTTTTTAAAGGCCTATCTGATTAGG
CCAGGCCCAAGTGAGCTTTAAGTCAACTGATTAGAGATCTTAATTAC
SG13S183

CTGAAGCTCAGGATTCTCTTCCAAGCTCACTGGTTGTTGGCAGAAT
TCAGTTCTTTCCAGTTGGAAGACTAAAGCCTACAGTCTTCAGTCTCTAGAA
GCCTTTTCTCTGGCACAGGTTTCTCTACAACATGGCCATTTATGTCTTTAA
GGCCAATAGGAGAACATGATTAGCATATTTTTTTTAAAGTGAACCTTTAGAC[
C/T]CTTTTTTAAAGGCCTATCTGATTAGGCCAGGCCCAAGTGAGCTTTAAG
TCAACTGATTAGAGATCTTAATTACATCTGCAAAGTCCCTTCATGTTTACC
GTATAACATAACTTAGTGAAAGGAGTGAAATTGCAACCAGGTTCTGCCTG
CACTCCACGGAAGGGGATTCTGCAGAAGTGTGGGTACGGGGGGGGTTA
SG13S184

AGAACATGATTAGCATATTTTTTTTAAAGTGAACCTTTAGACCTTTTTT
TAAAGGCCTATCTGATTAGGCCAGGCCCAAGTGAGCTTTAAGTCAACTGA
TTAGAGATCTTAATTACATCTGCAAAGTCCCTTCATGTTTACCGTATAACA
TAACTTAGTGAAAGGAGTGAAATTGCAACCAGGTTCTGCCTGCACTCCAC[
A/G]GAAGGGGATTCTGCAGAAGTGTGGGTACGGGGGGGGTTATTTTGGGA
TTCTGCCTACGTCACTGAGTCAAAAGAAGCTGAATGGTTGTGATGCTGAG
GTTTTTGGGCAGCAGCAGTGTGTGTGTGTGAGTGAATTCATACGTATGACC
ACCTGGGAAGAAAGGAGGCTGTGGTTTCCTCCACCTCCTGGCAGACAGA
SG13S185

GGGATTACAGACACACACTGCCACGCCTGGCTAATTTTTGTATTTTT
AGTAGAGACGAGGTTTTGCCATGTTGGCCAGGCTGGTCTTGAACCTCCTGA
CCTCAAGTGATCCGCCCACCTCAGCCTCCCAAAGTGCTGGGATTACAGAC
GTGAGCCACCATTAACCATTTTTCTATCTCCTGTGGGAAAGGGCACAGTG
A[A/G]AGAACAGATGAAGCTGAGACATACAAGTGAACCTCCTCCCTCCTCTC
CATTTAGACTAAAATAGGATTATTCATACTGAGATTCTCCCTGGTTGCAAA
GAGATAATCTGTGCAACTGGGTTTTTACAATTATCCCTACCCTATGCTTTC
CTCATCTGTCTTCCTCGTAGTCAGCTCAGGCTGCTATAACAAAACACCA
SG13S405

GGCAGATTCCGGTGTCTAATGAGGTCCTGCTTCCAGTTTATAGACA
GTGCCTTATCGCTACCGCCTTACACAGTGGAAGGAGAGGACGAGAAGCTC
CTTGGGCTTTTTTTTTGTTTCTTTCTTCTCTCTCTCTTTTTTTTTTTTT
AATAAGGTCATATCTTAGTCCATTTTGTGTTGCTAAAAGGAACATCT[A/G
]AGGTTGAGTAATTTATTTTATTTTAAAAAGTGGCCAGGCATGGAGGCTTA
TCCTGTAACCTAATCCTTTAGGAGGCCAAAACAGCAGGATTGTTTGAGG
CCAGGAGTTCAAGACCAGCCTAGGCAAGATAGTGAGACCCCATCTACCCC
ATCTCTACTAAAATTTTAAAAAATTAGCTGTGTGTTGTAAAGTGTGC
SG13S91

AATTTATTTTATTTTAAAAAGTGGCCAGGCATGGAGGCTTATCCTGT
AACCCTAATCCTTTAGGAGGCCAAAACAGCAGGATTGTTTGAGGCCAGGA
GTTCAAGACCAGCCTAGGCAAGATAGTGAGACCCCATCTACCCCATCTCT
ACTAAAATTTTAAAAAATTAGCTGTGTGTTGTAAAGTGTGCTTGTAGTCCC
[A/G]GCCACTTGAGAGGCTGAGGTGGGTGGAGTTCAAGGCTGCAGTGAGT
TATGATTGAGCCACTGCACTCCAACCCGGGTAAACGGGGCAAGACCTTGTC
TCTATTTAAAAAATAAATCTTTATGTGGCTCACTATTCTGGGTGGCTGG
AAAGTTCAAGATTGGGCATCTGCATCTGGTGACAGCCTCATGTCGCTTCC
SG13S186

TAACCCTAATCCTTTAGGAGGCCAAAACAGCAGGATTGTTTGAGGC

FIG. 8.36

CAGGAGTTCAAGACCAGCCTAGGCAAGATAGTGAGACCCCATCTACCCCA
TCTCTACTAAAATTTTAAAAAATTAGCTGTGTGTTGTAAAGTGTGCTTGTA
GTCCCGGCCACTTGAGAGGCTGAGGTGGGTGGAGTTCAAGGCTGCAGTGA
G[A/T]TATGATTGAGCCACTGCACTCCAACCCGGGTAACGGGGCAAGACCT
TGTCTCTATTTAAAAAATAATCTTTATGTGGCTCACTATTCTGGGTGG
CTGGAAGATTCAAGATTGGGCATCTGCATCTGGTGACAGCCTCATGTGCG
TTCCAGTCATGGGGGAAGACGAAGGAGAGCTGGCACGTGCAGATATCAC
G

SG13S187

ATCCTTTAGGAGGCCAAAACAGCAGGATTGTTTGAGGCCAGGAGTT
CAAGACCAGCCTAGGCAAGATAGTGAGACCCCATCTACCCCATCTCTACT
AAAATTTTAAAAAATTAGCTGTGTGTTGTAAAGTGTGCTTGTAAGTCCC
CACTTGAGAGGCTGAGGTGGGTGGAGTTCAAGGCTGCAGTGAGTTATGAT
T[A/G]AGCCACTGCACTCCAACCCGGGTAACGGGGCAAGACCTTGTCTCTA
TTAAAAAATAATCTTTATGTGGCTCACTATTCTGGGTGGCTGGAAA
GTTCAAGATTGGGCATCTGCATCTGGTGACAGCCTCATGTGCGCTTCCAGTC
ATGGGGGAAGACGAAGGAGAGCTGGCACGTGCAGATATCACGTGTTGAG
G

SG13S188

TTAAAAAATTAGCTGTGTGTTGTAAAGTGTGCTTGTAAGTCCC
ACTTGAGAGGCTGAGGTGGGTGGAGTTCAAGGCTGCAGTGAGTTATGATT
GAGCCACTGCACTCCAACCCGGGTAACGGGGCAAGACCTTGTCTCTATTT
AAAAAATAATCTTTATGTGGCTCACTATTCTGGGTGGCTGGAAAGTT
CA[A/G]GATTGGGCATCTGCATCTGGTGACAGCCTCATGTGCGCTTCCAGTC
ATGGGGGAAGACGAAGGAGAGCTGGCACGTGCAGATATCACGTGTTGAG
GGCAGAAGCGAGAGAGAGAGGGGAGAGATGCCAGGCTCTTTTAAACAAC
CAGCACTGGGGAACTAATAGAGTGAGAGCTCACTGACTCCTGAGGGAG
GACAT

SG13S406

ATGGGGGAAGACGAAGGAGAGCTGGCACGTGCAGATATCACGTGT
TGAGGGCAGAAGCGAGAGAGAGAGGGGAGAGATGCCAGGCTCTTTTAA
CAACCAGCACTGGGGAACTAATAGAGTGAGAGCTCACTGACTCCTGAGG
GAGGACATTAATCTATTGATGAGCGACCTGCCTCCATGACCCAAACACCT
CCAA[C/T]GATACCCACCTCCAACACTGCCACACTAGGGATTAACTTTCA
ACTTGAGATTTAGAGGGGGGAACTTACAAACTATCGCAGGCACTAATAC
CACTCATGAGGGCTCCACCTTCATGACCTAATCACTTCCTAAAGGCCTTAC
CTCTTAATCTCATCACATTGAGGATTCGATTTCAACTTGAATTTTGGGGGG
AC

SG13S92

CTCGCTGCCACCTGAAATTAGATCATTTATTTACCCCTTTATTTGTT
CAGTTTGCCTTGTCCGTTAGAATATAAGCTTCCAAAGGGCAGGAGCTTTGC
CTATATTGTTAGGCCGGGCATACAATGAGCACTCAAAAAAATATTTGATG
AGTGTATGAAAGAACAGACTGGGTTATGTAATTGTGCCTACTTACCTATA[
C/T]GACCGTGTGGTGGGGTTTATGGTGGGTGTGGTGGTGTGCTATAGG
GCTATAAGCAAATTTGGGACAGGGAGTCTAAGAAATGTTCTTAAATTTTA
GTAAGCAAAGCATCCTCTACAGAACCTGTCTTAAACATGAAAGTTCCTT
AGTGCTACCCCCAGAGGTATGATTTGGTAGGTCAAGGATAGGGCCTGGAA
SG13S93

TGCCACCTGAAATTAGATCATTTATTTACCCCTTTATTTGTTTCAGTT
TGCCTTGTCCGTTAGAATATAAGCTTCCAAAGGGCAGGAGCTTTGCCTATA

FIG. 8.37

TTGTTAGGCCGGGCATACAATGAGCACTCAAAAAAATATTTGATGAGTGT
ATGAAAGAACAGACTGGGTTATGTAATTGTGCCTACTTACCTATATGACC[
A/G]TGTGGTGGGGTTTATGGTGGGTGTGGTGGTGATGGCTATAGGGCTAT
AAGCAAATTTGGGACAGGGAGTCTAAGAAATGTTCTTAAATTTTAGTAAG
CAAAGCATCCTCTACAGAACCTGTCTTAAACATGAAAGTTCCTTAGTGCT
ACCCCCAGAGGTATGATTTGGTAGGTCAAGGATAGGGCCTGGAAATTCA
SG13S36

CCTGTCTTAAACATGAAAGTTCCTTAGTGCTACCCCCAGAGGTAT
GATTTGGTAGGTCAAGGATAGGGCCTGGAAATTCACATTCTTGTTAAGAT
GTTCTTCATCCGGGGTTTGTTGACCACCTTTTCAGAAGATTTTGTCTGTGA
GCTGTACTACCCAATGCAGTAGTTCGTAGTCAGTGTGGCTCCTGAGCCCT[
C/T]GAAGTGTAGCTCCTCTGAACTGAGACGTGCTGTAAATGTAAATTGCA
CACCGGAGTTTGAAGAGTTAATACAAAGAAAAAGGAATGCAAAACATCT
CATTAATAATGCTTTACACTGATTACATATTGAAATGGTAATCTTGTAGAT
ATAGTGC GTTAAATAAAATATACTGTTAGGCTTAATTTACAGTCTTTATA
SG13S407

TCAGCCAATCAACAAGAGGGCAAAAGAACAACATTTGATGTGTA
ATTACTTAATTTAGTGCATATGCATTTGGGTCCTCAATGTCAGCACTATGG
CAACCAGAACATGGCCACAATAACTGTCTGGAAATGTCTATTCTTACCTG
GACCCAGCAGGCCATGCCCCACTGATTATATAATCTCCCTCTCTCCTTGTT
A[C/T]GGTCTGAATGCTTGCATCCCTCAAAAATTCATGTGTTGAAATCCTA
ACCCCAAGGTGATGATATTAGGAGGTGCGCCTTTTGAGAGGTAATTAGG
TCATGAAGACAGCATCCTCATGAATGGGATTAGTGTCTTATAAAATAGG
CCCAAGGGAGCTCATTCACTTTGTCCACCATGTGAGAACACAGCGAGAGG
G

SG13S408

CCTTGTTACGGTCTGAATGCTTGCATCCCTCAAAAATTCATGTGTTG
AAATCCTAACCCCAAGGTGATGATATTAGGAGGTGCGCCTTTTGAGAGG
TAATTAGGTCATGAAGACAGCATCCTCATGAATGGGATTAGTGTCTTATA
AAATAGGCCCAAGGGAGCTCATTCACTTTGTCCACCATGTGAGAACACAG
[C/T]GAGAGGGCACCATTTATGCACCAGGAAATGGGCCTTTTCCAGACAAT
CTGTCCGTGCCTGGATCTTGGACTTCACAGCCTCTAGAACTGTGAGAAAT
AATTTGTTTTTTTATAAGCCACCAAATCTATGGTTTTTTTTTATAGAAACCGTA
ATGGACTAAAACACTCCCTAATTATATTTAACTTATCAGTGCCTG
SG13S7

CTAACCCCAAGGTGATGATATTAGGAGGTGCGCCTTTTGAGAGGT
AATTAGGTCATGAAGACAGCATCCTCATGAATGGGATTAGTGTCTTATA
AAATAGGCCCAAGGGAGCTCATTCACTTTGTCCACCATGTGAGAACACAG
CGAGAGGGCACCATTTATGCACCAGGAAATGGGCCTTTTCCAGACAATCT
GT[C/T]GGTGCCTGGATCTTGGACTTCACAGCCTCTAGAACTGTGAGAAAT
TAATTTGTTTTTTTATAAGCCACCAAATCTATGGTTTTTTTTTATAGAAACCGT
AATGGACTAAAACACTCCCTAATTATATTTAACTTATCAGTGCCTGGGC
AGTGACATATTAAGAAGATGCTGGCCAACGTAATTGACACCATAAGGCT
SG13S37

TCATCTCATTTTAACTTTTGTCTTCAAAGCCTCTCTTTTCATGACTTC
CCCGCCTTCATTTTTCCCATATGGTGGGGTTATTATTAAGACATTAAATGA
GAGTGGACAGGTAGGCAAAGGAGGTGGGTTGCAGGGGAGTTGAGGGTTG
CCTGTGTACTTTTCTAGACTGTTCCACTTCACATCAGTGAAATATTTCCA[A
/G]TTGATACTATCATGAAACAAAGCAAATGAAATGCTGAGCACGGAGCTT
CGTCTTGATGAAATGCTGAAAGAAAAGAAAGGAAAAATAAAGTAGCCAT

FIG. 8.38

TATTTTGGCCCTTCCTCCCACCCCATGTTTACTACTCTTATTTCTCTTTTGT
ATTGTTGTGTTGGAAGCACAGCATCAGAAAACTCCCAGTTTGA
SG13S409

ACAGGTAGGCAAAGGAGGTGGGTTGCAGGGGAGTTGAGGGTTGCC
TGTGTACTTTCTAGACTGTTCCACTTCACATCAGTGAAATATTCCCAATT
GATACTATCATGAAACAAAGCAAATGAAATGCTGAGCACGGAGCTTCGTC
TTGATGAAATGCTGAAAGAAAAGAAAGGAAAAATAAAGTAGCCATTATTT
TT[A/G]CCCTTCCTCCCACCCCATGTTTACTACTCTTATTTCTCTTTTGTAT
TGTTGTGTTGGAAGCACAGCATCAGAAAACTCCCAGTTTGAAGAGATAA
CTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGATGCCACCG
TGAGGTCCAGGACGTAAAGAGGAAAAAAACAGACAAAAAAATCCATATG
A

SG13S8

CAGGTAGGCAAAGGAGGTGGGTTGCAGGGGAGTTGAGGGTTGCCT
GTGTACTTTCTAGACTGTTCCACTTCACATCAGTGAAATATTCCCAATTG
ATACTATCATGAAACAAAGCAAATGAAATGCTGAGCACGGAGCTTCGTCT
TGATGAAATGCTGAAAGAAAAGAAAGGAAAAATAAAGTAGCCATTATTT
TG[A/C]CCTTCCTCCCACCCCATGTTTACTACTCTTATTTCTCTTTTGTATT
GTTGTGTTGGAAGCACAGCATCAGAAAACTCCCAGTTTGAAGAGATAAC
TCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGATGCCACCGT
GAGGTCCAGGACGTAAAGAGGAAAAAAACAGACAAAAAAATCCATATGA
A

SG13S410

TTCGTCTTGATGAAATGCTGAAAGAAAAGAAAGGAAAAATAAAGT
AGCCATTATTTTGGCCCTTCCTCCCACCCCATGTTTACTACTCTTATTTCT
CTTTTGTATTGTTGTGTTGGAAGCACAGCATCAGAAAACTCCCAGTTTGA
AGAGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGA
[C/T]GCCACCGTGAGGTCCAGGACGTAAAGAGGAAAAAAACAGACAAAA
AAATCCATATGAAATGAAATGTGAAAGAGGCGCTTTCGAGCAGATGAGT
GTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGCTGCA
CCTGGCGGGATAAACACTGGTCTAACAGAGGATCCTTGTTTCAAGGAGGC
T

SG13S411

AAGAAAAGAAAGGAAAAATAAAGTAGCCATTATTTTGGCCCTTCCT
CCCACCCCATGTTTACTACTCTTATTTCTCTTTTGTATTGTTGTGTTGGA
GCACAGCATCAGAAAACTCCCAGTTTGAAGAGATAACTCAGTGTTTAGT
TCACTTAAACCTGAGAAAGGAGAAGAGGATGCCACCGTGAGGTCCAGGA
C[A/G]TAAAGAGGAAAAAAACAGACAAAAAAATCCATATGAAATGAAAA
TGTGAAAGAGGCGCTTTCGAGCAGATGAGTGTTGTAGATTACAGTGTTGA
GAGCTGTTTGTGTCCAGAGCTGCTTGCTGCACCTGGCGGGATAAACACTG
GTCTAACAGAGGATCCTTGTTTCAAGGAGGCTGCCTTTTATTTGGGGGGAC
AA

SG13S9

ATTATTTTGGCCCTTCCTCCCACCCCATGTTTACTACTCTTATTTCT
CTTTTGTATTGTTGTGTTGGAAGCACAGCATCAGAAAACTCCCAGTTTGA
AGAGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGA
TGCCACCGTGAGGTCCAGGACGTAAAGAGGAAAAAAACAGACAAAAAA
[C/T]CCATATGAAATGAAATGTGAAAGAGGCGCTTTCGAGCAGATGAGT
GTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGCTGCA

FIG. 8.39

CCTGGCGGGATAAACTGGTCTAACAGAGGATCCTTGTTTCAAGGAGGC
TGCCTTTTATTTGGGGGGACAAAATTGTTCTTGAAAGCTGCTCAGTGGT
SG13S412

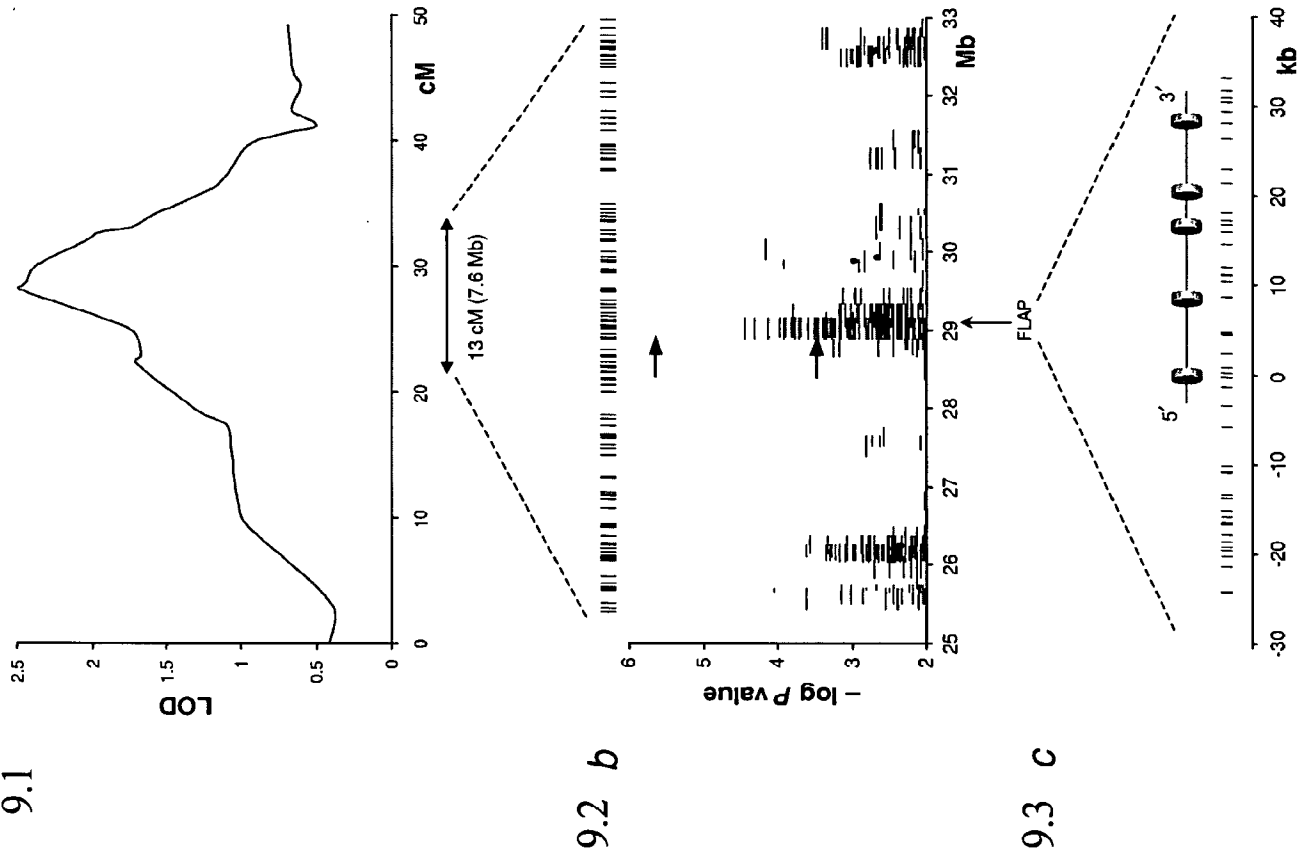
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GTT[A/G]TAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGCT
GCACCTGGCGGGATAAACTGGTCTAACAGAGGATCCTTGTTTCAAGGA
GGCTGCCTTTTATTTGGGGGGACAAAATTGTTCTTGAAAGCTGCTCAGTGG
TTCAAGCTACAGCATGGTGGACTAGCAGAATGGACTCCAGGGCCTCCGAG
GA

SG13S413

TTTTGAGAGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGG
AGAAGAGGATGCCACCGTGAGGTCCAGGACGTAAAGAGGAAAAAACAG
ACAAAAAATCCATATGAAATGAAAATGTGAAAGAGGCGCTTTCGAGCA
GATGAGTGTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCT
TGC[C/T]GCACCTGGCGGGATAAACTGGTCTAACAGAGGATCCTTGTTT
CAAGGAGGCTGCCTTTTATTTGGGGGGACAAAATTGTTCTTGAAAGCTGCT
CAGTGGTTCAAGCTACAGCATGGTGGACTAGCAGAATGGACTCCAGGGCC
TCCGAGGAGACAGTGACTGCTGCCAGAAATAGTCAAGGATAGAAAGGAA
GGA

FIG. 8.40

FIG. 9



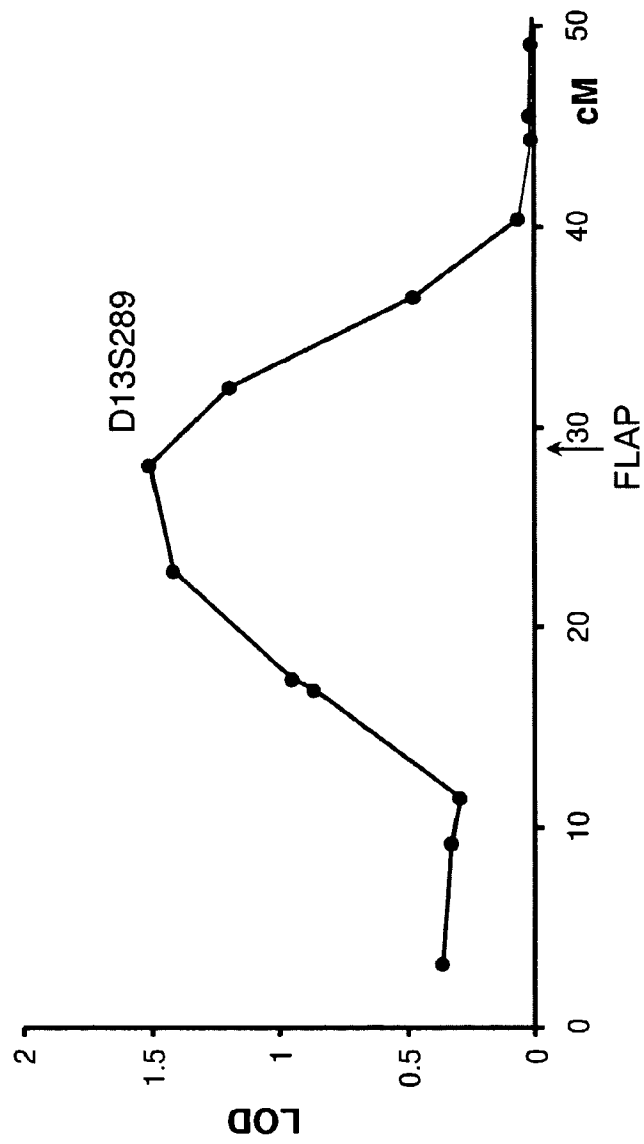


FIG. 10

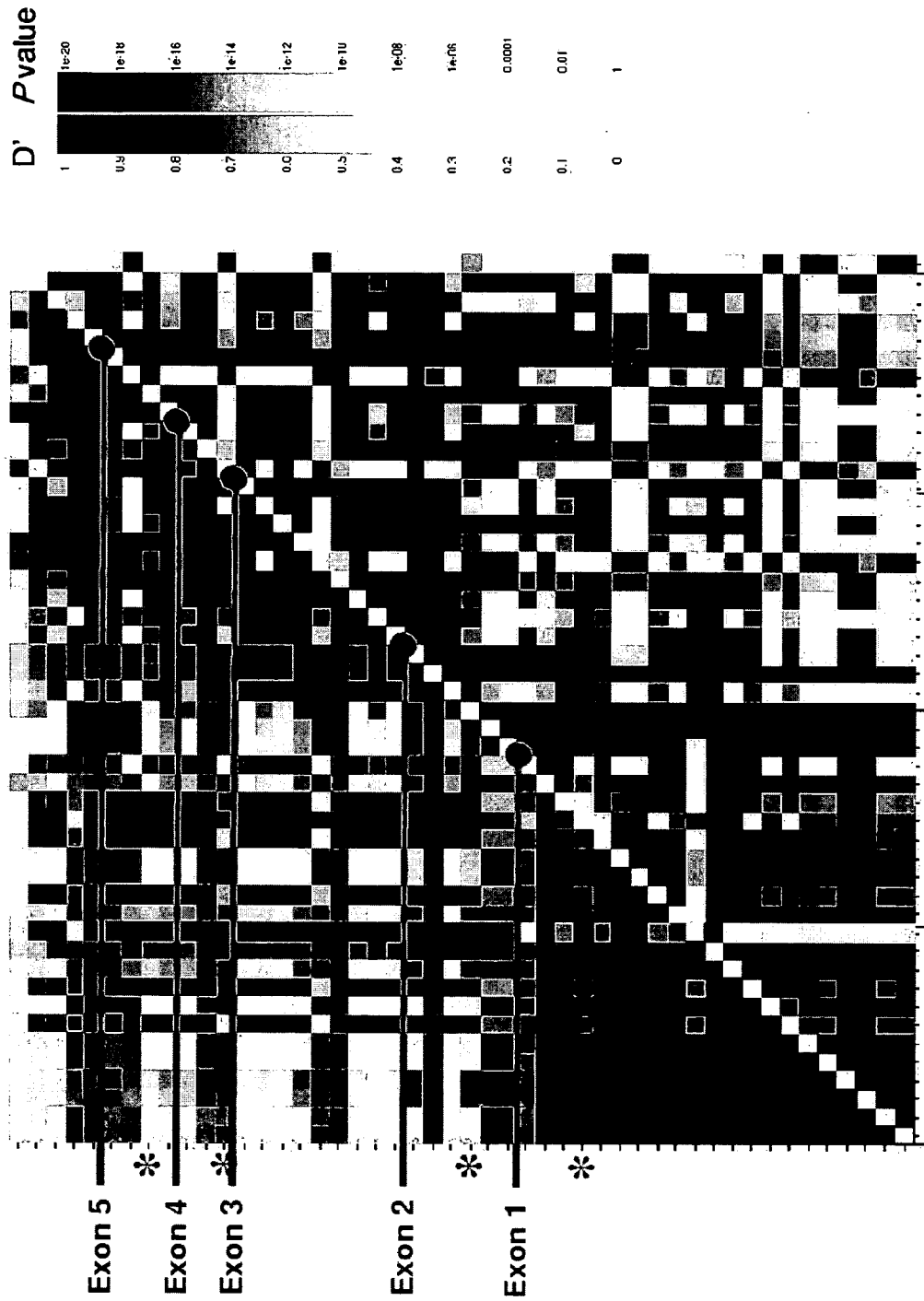


FIG. 11